

EXERCISE AND BLOOD FLOW RESTRICTION

ZACHARY K. POPE,¹ JEFFREY M. WILLARDSON,¹ AND BRAD J. SCHOENFELD²

¹*Kinesiology and Sports Studies Department, Eastern Illinois University, Charleston, Illinois; and* ²*Department of Health Sciences, Lehman College, Bronx, New York*

ABSTRACT

Pope, ZK, Willardson, JM, and Schoenfeld, BJ. Exercise and blood flow restriction. *J Strength Cond Res* 27(10): 2914–2926, 2013—A growing body of research has demonstrated the effectiveness of exercise (low-intensity resistance training, walking, cycling) combined with blood flow restriction (BFR) for increased muscular strength and hypertrophy. The BFR is achieved via the application of external pressure over the proximal portion of the upper or lower extremities. The external pressure applied is sufficient to maintain arterial inflow while occluding venous outflow of blood distal to the occlusion site. With specific reference to low-intensity resistance training, the ability to significantly increase muscle strength and hypertrophy when combined with BFR is different from the traditional paradigm, which suggests that lifting only higher intensity loads increases such characteristics. The purpose of this review was to discuss the relevant literature with regard to the type and magnitude of acute responses and chronic adaptations associated with BFR exercise protocols vs. traditional non-BFR exercise protocols. Furthermore, the mechanisms that stimulate such responses and adaptations will be discussed in the context of neural, endocrine, and metabolic pathways. Finally, recommendations will be discussed for the practitioner in the prescription of exercise with BFR.

KEY WORDS hypoxia, KAATSU, metabolic acidosis, hypertrophy, strength, growth hormone

INTRODUCTION

Blood flow restriction (BFR) as an accessory to a variety of different exercise modes (e.g., resistance exercise, walking, cycling) has recently become a popular research topic. The BFR during exercise typically involves the application of pressurized cuffs to the proximal portion of each lower extremity

(i.e., inguinal crease [48,90]) or upper extremity (i.e., distal to the deltoid muscle [91]). Resistance exercise research on this topic has typically tested relatively low intensities (i.e., 20–30% of 1 repetition maximum [1RM]), high repetitions per set (i.e., 15–30), and short rest intervals between sets (i.e., 30 seconds [91]). Lastly, research has commonly examined single joint exercises (e.g., plantar flexion, elbow flexion, leg extension [76,90]) to minimize the complexity of the movement pattern with the blood flow partially restricted.

Research has demonstrated that BFR exercise training resulted in increased muscular strength (27,49,61,83,91), hypertrophy (1,37,49,90,91), localized endurance (38,90), and cardiorespiratory endurance (1,72). The time course of these adaptations has been hypothesized to occur differently vs. traditional resistance training that incorporates heavier loads without the application of BFR (55). Hypothetically speaking, the potential mechanisms for these adaptations may include (a) hypoxia-induced additional or preferential recruitment of fast-twitch (FT) muscle fibers, (b) greater duration of metabolic acidosis via the trapping and accumulation of intramuscular protons (H⁺ ions) and stimulation of metaboreceptors, possibly eliciting an exaggerated acute systemic hormonal response, (c) external pressure-induced differences in contractile mechanics and sarcolemmal deformation, resulting in enhanced growth factor expression and intracellular signaling, (d) metabolic adaptations to the fast glycolytic system that stem from compromised oxygen delivery, (e) production of reactive oxygen species (ROS) that promotes tissue growth, (f) gradient-induced reactive hyperemia after removal of the external pressure, which induces intracellular swelling and stretches cytoskeletal structures that may promote tissue growth, and (g) activation of myogenic stem cells with subsequent myonuclear fusion with mature muscle fibers (70).

It should be noted that not all mechanisms appear active in all forms of BFR exercise. Loenneke et al. (51) hypothesized that adaptations such as strength, hypertrophy, and endurance associated with BFR exercise may take place in the absence of significant metabolite accumulation and systemic hormonal response or the additional recruitment of FT muscle fibers. The justification for this hypothesis was based on observations concerning the maintenance or increase in muscle strength and size for BFR protocols

Address correspondence to Dr. Jeffrey M. Willardson, jmwillardson@eiu.edu.

27(10)/2914–2926

Journal of Strength and Conditioning Research
© 2013 National Strength and Conditioning Association

conducted without exercise or in conjunction with walking. Under such conditions, there is no significant metabolite accumulation or systemic hormonal responses. It was concluded that cell swelling caused by reactive hyperemia might be a common mechanism present with all forms of BFR exercise that stimulates muscular adaptations.

Perhaps the key aspect of BFR training is the unexpectedly low relative intensity at which the adaptations are stimulated to occur. Numerous studies examining BFR reported increased muscle cross-sectional area (CSA) and strength after BFR plus walking (2), BFR plus cycling (1), BFR plus body weight circuit training (37), and BFR plus resistance training with 20% of a 1RM load (5)—far below the typical intensities thought necessary to induce hypertrophic and strength adaptations (7). However, it should also be noted that the application of BFR in the absence of exercise has been shown to prevent reductions in muscle strength and size because of prolonged periods of disuse and immobilization. The purpose of this review will be to discuss the relevant literature with regard to the type and magnitude of acute responses and chronic adaptations associated with BFR in conjunction with different exercise modes protocols vs. traditional non-BFR exercise modes. Furthermore, the mechanisms that stimulate such responses and adaptations will be discussed in the context of neural, endocrine, and metabolic pathways. Finally, recommendations will be discussed for the practitioner in the prescription of BFR exercise.

HEMODYNAMICS AND BLOOD FLOW RESTRICTION

Application of External Pressure

The BFR has been achieved via the application of a tourniquet (83), pressurized cuff (88), or elastic banding (53). The external pressure applied is sufficient to maintain arterial inflow while occluding venous outflow of blood distal to the occlusion site. Early studies that tested responses to BFR used pressures >250 mm Hg (83), yet significant adaptations have been demonstrated with pressures as low as 50 mm Hg (86).

Takano et al. (88) found that a pressure of 160–180 mm Hg with a 33-mm-wide cuff resulted in an approximate 30% reduction in arterial blood flow vs. that observed in a resting seated position. It has been demonstrated that as cuff width increases, the pressure requirements to achieve a given percentage of restricted blood flow decreases (17,52). The restricted blood flow (88) reduces intramuscular oxygen delivery (92) and decreased venous clearance of metabolites (36), leading to exaggerated levels of metabolic acidosis and an earlier onset of peripherally mediated fatigue as demonstrated in reduced time under tension and significantly fewer repetitions during resistance exercise sets (54,96). However, it should be noted that BFR plus walking or BFR in the absence of exercise does not result in a significant accumulation of metabolites, indicating that other mechanisms, such as reactive hyperemia, might account for adaptations associated with these modes of BFR. The succeeding sections

will discuss studies that assessed various physiological responses and adaptations via BFR in conjunction with different types of exercise alone or in comparison with traditional exercise modes.

Muscle Oxygenation

Tanimoto et al. (92) compared 3 sets of knee extensions (30 repetitions performed during the first set; the second and third sets were performed for repetition maximums with 1-minute rest intervals between sets) under 4 conditions—(a) low-intensity (30% of 1RM) with BFR (200 mm Hg; cuff width not reported), (b) low-intensity (50% of 1RM) with controlled velocity (i.e., 3-second eccentric, 3-second concentric, 1-second pause), (c) low-intensity (50% of 1RM) with isometric actions, and (d) high-intensity (80% of 1RM) with normal movement—to assess muscle oxygenation. The authors found that the low-intensity with BFR condition (i.e., session “a”) elicited the greatest decrease in mean minimal muscle oxygenation (~22% of baseline) during exercise, whereas sessions b, c, and d elicited decreases of approximately 24, 28, and 36% of the baseline, respectively. Furthermore, the mean maximal muscle oxygen values postexercise were approximately 143, 122, 105, and 121% of the baseline value. These results indicate that the greatest degree of blood reperfusion occurred after the BFR condition.

The trapping of metabolites via an occlusive stimulus creates a pressure gradient favoring the flow of blood into the muscle fibers (intracellular space). This enhanced reperfusion and subsequent intracellular swelling are believed to threaten the structural integrity of the cell membrane, promoting an anabolic response (51). There is a large body of evidence indicating that cell swelling promotes an increase in protein synthesis and a decrease in proteolysis in a variety of different cell types including hepatocytes, osteocytes, breast cells, and muscle fibers (46,58). It also has been hypothesized that an increase in myocellular hydration may trigger the proliferation and fusion of satellite cells to promote hypertrophy (18). In combination, these factors could conceivably help to mediate hypertrophic adaptations pursuant to exercise with BFR.

A recent study by Gundermann et al. (33), however, found that the infusion of a pharmacological vasodilator into the femoral artery immediately after BFR exercise did not increase muscle protein synthesis to a greater extent than BFR exercise alone did, suggesting that reperfusion might not be the key stimulus promoting the hypertrophic response to BFR training. However, the study was limited by the fact that the researchers could not accurately reproduce the immediate (first ~10 minutes) postexercise hyperemic response, making it difficult to assess whether or not the initial signal from cellular hydration plays a role in anabolism. Further research is required to shed more light on this topic.

Hyperoxia (i.e., excessive tissue oxygenation) is known to generate ROS (i.e., hydrogen peroxide [H₂O₂], hypochlorous

acid [HOCl]) that can cause cell injury via lipid peroxidation (LP), enzyme inactivation, and DNA damage (11) upon reperfusion. However, distinctions have been made between ROS produced chronically during resting conditions, where radicals are primarily generated by the mitochondrial electron transport chain in the beta-oxidation of fatty acids, and those generated transiently by contracting muscles during exercise (6). The ROS have been shown to promote growth in both smooth muscle and cardiac muscle (87), and several researchers have speculated that they might be involved in the hypertrophic response pursuant to BFR (92,94,97). Hornberger et al. (35) demonstrated that selenoprotein-deficient transgenic mice exhibited significantly greater increases in exercise-induced muscle growth compared with that in wild-type controls, suggesting an ROS-mediated hypertrophic effect through redox sensitive signaling pathways. Conversely, there is evidence that ROS may have a negative effect on various serine and threonine phosphatases, including calcineurin (13). Given that calcineurin has been shown to mediate muscle hypertrophy (20,66), elevated ROS levels may in fact interfere with the growth process. The topic is obviously complicated, and there remain large gaps in our knowledge base at this time.

Although hypoxia and subsequent reperfusion associated with arterial occlusion have been shown to increase ROS levels (41,93), results have not been consistent in studies investigating BFR exercise. Takarada et al. (89) reported that concentrations of lipid peroxide were not significantly different between a BFR group compared with those performing the same exercise without BFR. Similarly, Goldfarb et al. (28) found that although partial occlusion alone increased levels of protein carbonyl, a marker of ROS stress, the response was attenuated when low-intensity resistance was combined with BFR. The reasons for these discrepant findings are not clear at this time. Further research is warranted to elucidate whether ROS play a role in postexercise muscle adaptations pursuant to BFR and, if such a role does in fact exist, to determine whether these adaptations display a dose-response relationship.

CARDIOVASCULAR RESPONSES AND ADAPTATIONS

Heart Rate and Stroke Volume

The BFR has been shown to alter cardiac output during walking (77), and resistance exercise (88), yet might be dependent on the mode and level of exertion (e.g., submaximal vs. exhaustive) (54). Renzi et al. (77) found that, during walking with BFR, the restriction to venous return and increased vascular resistance was manifested in a reduced stroke volume (SV) and simultaneous increase in the heart rate (HR) to maintain cardiac output. Other research (3,88) has also confirmed an increased HR response.

Kacin and Strazer (38) evaluated isoinertial endurance via dynamic knee extensions under 2 conditions: (a) 15% of maximal voluntary contraction (MVC) without BFR, (b) 15% of MVC with BFR at 230 mm Hg (13-cm cuff width);

the BFR condition was performed to repetition failure, whereas the non-BFR condition was performed for submaximal repetitions to equate the total volume for each protocol. The authors found that both conditions similarly elevated HR to approximately $200 \text{ b} \cdot \text{min}^{-1}$ at 10 seconds postexercise. Furthermore, Loenneke et al. (54) observed similar HR responses during 2 sets of bilateral knee extensions to failure, at 30% of 1RM with BFR via elastic knee wraps and without BFR. Collectively, these findings indicate that an increased HR response may be inevitable with or without BFR when exercise is performed to repetition failure.

Blood Pressure

Research examining blood pressure response to BFR exercise has varied. Renzi et al. (77) observed a substantial increase in diastolic, systolic, and mean blood pressures during walking with BFR. Double product (index of myocardial oxygen demand) was 3-fold higher during the BFR session vs. the control (77). Yet, Kacin and Strazer (38), discussed previously, found that both (Isch and Con) conditions similarly increased systolic, diastolic, and mean arterial pressures to roughly approximately 200, 120, and 150 mm Hg, respectively, at 10 seconds after repetition failure. Based on these findings, it appears that the type of training (walking vs. knee extension) and level of exertion (submaximal effort vs. repetition failure) might determine whether BFR training poses any additional or excessive demand on the cardiovascular system and caution should be exercised (e.g., less external pressure, less time under pressure, less exertion) for individuals with any form of cardiovascular disease.

Rossow et al. (79) compared postexercise (30 and 60 minutes) blood pressure responses in normotensive subjects after lower-body resistance exercise (i.e., leg press, knee flexion, knee extension, and plantar flexion) under 3 conditions; high-intensity (70% of 1RM; 3 sets of 10 repetitions; 1-minute rest intervals between sets), low-intensity (20% of 1RM; 4 sets; 30 repetitions first set; 15 repetitions sets 2, 3, and 4; 30-second rest intervals between sets), and the low-intensity protocol with the application of BFR (200 mm Hg; 5-cm cuff width). The authors found that only the high-intensity resistance exercise protocol induced a significant postexercise hypotensive (PEH) response. A potential flaw in the procedures was that the total volume of exercise (load \times sets \times repetitions) was not reported or compared between groups (e.g., 120 repetitions low-intensity condition vs. 30 repetitions high-intensity condition), which may account for the differences in the PEH response.

It should also be emphasized that the Rossow et al. (79) subjects were already normotensive to begin with. It would have been expected for hypertensive individuals to exhibit a hypotensive response. An accumulating PEH response, from reductions in peripheral vascular resistance, might be important in obtaining a longitudinal reduction in blood pressure. However, high-intensity resistance training is contraindicated for hypertensive individuals and future research

should examine potential reductions in blood pressure for hypertensive individuals with consistent application of BFR during resistance training.

Vascular Function

Research examining measures of vascular function in conjunction with BFR has been inconsistent. One such measure, arterial compliance, has been examined in both acute and longitudinal studies. Renzi et al. (77) examined hemodynamics and endothelial function before and 20 minutes after walking with and without continuous BFR (160 mm Hg; cuff width not reported). The exercise protocol consisted of 5 sets of 2-minute duration treadmill walking bouts with 1-minute rest intervals between sets. The authors found that systemic arterial compliance, indicative of the ability of vasculature to expand and retract during cardiac contraction and relaxation (determined via SV/pulse pressure ratio) decreased by 19% during the BFR condition vs. a 14% increase after the control condition; decreased arterial compliance has been associated with increased risk of cardiovascular disease. However, further research is needed to establish whether an acute reduction in arterial compliance is associated with long-term negative outcomes in cardiovascular health, especially for those with initial compromised cardiovascular function.

Conversely, short-term resistance training interventions have collectively indicated that the application of BFR does not negatively alter vascular function. Kim et al. (39) examined arterial compliance after a 3-week intervention that compared high-intensity lower-body (leg press, knee flexion, and knee extension) resistance training (80% of 1RM; 2 sets of 10 repetitions; 2-minute intervals between exercises; 1-minute rest intervals between sets) vs. low-intensity resistance training with BFR (20% of 1RM; 2 sets of 10 repetitions; 2-minute intervals between exercises; 1-minute intervals between sets). The authors found that neither high-intensity nor low-intensity with BFR resulted in decreased arterial compliance. Furthermore, there was a trend in the low intensity with BFR session (18% increase from baseline) toward an increased arterial compliance of the large arteries.

Similarly, 2 studies by Fahs et al. (21,22) examined acute and longitudinal responses in large and small arterial compliance and calf blood flow in recreationally active and healthy young men. In the first acute study (21), 3 bouts of resistance exercise were compared that included high intensity (70% of 1RM; 3 sets of 10 repetitions; 1-minute rest intervals between sets); and low intensity with and without BFR (20% of 1RM; first set 30 repetitions followed by 3 sets of 15 repetitions; 30-second rest between sets); the exercises performed in succession were the supine leg press, seated knee flexion, seated knee extension, seated plantar flexion. During the low intensity with BFR bout, the cuff width was 50 mm, and the pressure was 200 mm Hg. The results indicated that large arterial compliance had increased up to the 15-minute point after all the bouts. However, only the high-

intensity bout elicited an increase in small arterial compliance and calf blood flow.

In a subsequent longitudinal study carried over 6 weeks in the same sample, Fahs et al. (22) compared resistance training with 3 different training groups (and a nonexercise control group) for the same dependent variables as the previous acute study (21). All the training groups performed 3 workouts per week that consisted of 3 sets of 10 repetitions at 50% of 1RM for 4 upper body exercises (lat pulldown, seated shoulder press, elbow extension, and elbow flexion). However, the knee extension and knee flexion exercises were varied in this manner: high intensity (70% of 1RM; 3 sets of 10 repetitions; 1-minute rest between sets); moderate intensity (45% of 1RM; 3 sets of 15 repetitions; 1-minute rest between sets); low intensity with BFR (20% of 1RM; first set 30 repetitions followed by 3 sets of 15 repetitions; 1-minute rest between sets). The results indicated that calf blood flow (calf vascular conductance) was increased in all 3 groups compared with that in the control group without any changes in arterial compliance. The results from both these acute and longitudinal studies indicate the safety of low-intensity resistance exercise and training with BFR and indicate that from a longitudinal perspective it might be a suitable alternative to high-intensity resistance training for positive cardiovascular adaptations in normotensive individuals.

Patterson et al. (73) examined both resting and postocclusive blood flow (i.e., reactive hyperemia) before and after a 4-week, plantar flexion training intervention. The subjects were assigned to 1 of 2 matched groups based on plantar flexion 1RM. A moderate-intensity group (50% of 1RM; 3 sets to failure; 1-minute rest intervals between sets) and low-intensity group (25% of 1RM; 3 sets to failure; 1-minute rest intervals between sets) performed unilateral plantar flexion with continuous BFR (110 mm Hg; cuff width not reported) followed by a work-matched non-BFR protocol for the contralateral limb. The authors reported an increase in acute peak postocclusive calf blood flow for each group and only in the limb exercised in conjunction with BFR; no differences were reported for resting calf blood flow between conditions. The greater reactive hyperemia after BFR exercise may damage the endothelium; a potential concern for individuals with peripheral vascular disease and increased risk for thrombus formation. However, epidemiological research to date has indicated that the application of BFR during various exercise modes (walking, cycling, resistance training) is safe (15,69).

Cardiovascular repercussions must be accounted for in determining appropriate populations for which to incorporate BFR exercise training. Credeur et al. (16) reported that 4 weeks of BFR training (i.e., handgrip exercise) decreased brachial artery flow-mediated dilation (~30.36%). Additionally, Renzi et al. (77) found that a BFR session significantly decreased flow-mediated vasodilation of the popliteal artery. This decreased endothelial function might be indicative of ischemia-reperfusion injury to the vascular endothelium.

Therefore, more research is warranted to fully elucidate the vascular responses associated with BFR exercise and training. Although some effects of BFR training would be beneficial to cardiac populations (e.g., increased muscle strength and hypertrophy), other acute aspects might increase the risk of cardiac episode. A majority of research at this time has examined young, healthy individuals. More research is necessary to understand both the risks and benefits associated with BFR exercise and training for individuals with varying comorbidities.

Cardiorespiratory Endurance

Improvements to endurance capacity (i.e., increased oxidative enzymes, capillary density, SV, glycogen stores, and decreased HR) can be increased with the use of BFR training.

Abe et al. (1) examined BFR during cycling exercise in an 8-week study; the BFR group trained 3 sessions per week at 40% of $\dot{V}O_2\text{max}$ for 15 minutes with BFR (160–210 mm Hg; cuff width not reported), whereas the control group trained 3 sessions per week at 40% of $\dot{V}O_2\text{max}$ for 45 minutes without BFR. The key finding was that the BFR group improved $\dot{V}O_2\text{max}$ and time to exhaustion, 6.4 and 15.4%, respectively. Conversely, the control group exhibited a slight decrease in $\dot{V}O_2\text{max}$ (–0.1%) and smaller increase in time to exhaustion (3.9%). Posttraining measurements also indicated that the BFR group increased thigh and quadriceps muscle CSA and strength (3.4, 4.6, and 7.7%, respectively), whereas the control group did not demonstrate similar adaptations (0.1, 0.6, and 1.4%, respectively).

Similarly, Park et al. (72) found that in a group of Korean collegiate basketball players walking (4–6 $\text{km}\cdot\text{h}^{-1}$ at a 5% grade each set; total of 5 sets for 3 minutes each; 1-minute rest intervals between sets) with BFR (160–220 mm Hg; 110-mm cuff width) twice daily (6 sessions per week for 2 weeks) increased $\dot{V}O_2\text{max}$ (maximal graded exercise test via a cycle ergometer) and maximal minute ventilation, 11.6 and 10.6% respectively. Conversely, a work-matched control group without BFR did not experience improvements in these variables. These studies (1,72) suggest that the addition of BFR to common exercise modes (cycling, walking) increases cardiorespiratory endurance and with perhaps shorter duration per session vs. traditional longer duration prescriptive approaches.

NEUROMUSCULAR RESPONSES AND ADAPTATIONS

Localized Muscular Endurance

Given that localized muscular endurance is defined as the capacity to continue submaximal muscle actions over extended durations, and is typically developed in relative terms at lower training intensities (12), the application of BFR training might be especially useful in this regard. The hypoxic intramuscular condition promoted via BFR may stimulate increases in capillarization with implications for subsequent improvements in localized muscular endurance

performance. Larkin et al. (47) used the unilateral knee extension with or without the addition of BFR to examine the postexercise serum levels of vascular endothelial growth factor (VEGF)—a key growth factor that upregulates angiogenesis or capillary formation. In addition to protein expression of VEGF, mRNA transcripts indicative of angiogenesis were also examined, including: VEGF and its primary receptor (VEGF-R2), hypoxia-inducible factor 1 alpha (HIF-1 α), and isoforms of nitric oxide synthase (NOS).

Larkin et al. (47) tested subjects on 2 occasions (separated by 3 weeks) in a randomized crossover design; each exercise bout consisted of 10 sets of 12 repetitions of unilateral knee extensions with the dominant limb, at 40% of 1RM, and with 1-minute rest intervals between sets. For the BFR condition, an external cuff was placed around the proximal thigh and inflated to 220 mm Hg (cuff width not specified). The key finding was that the BFR condition elicited significantly greater angiogenic responses vs. the non-BFR condition. The BFR condition resulted in significantly greater levels of deoxygenated hemoglobin in the vastus lateralis (assessed via near infrared spectroscopy) during exercise—an indicator of muscle hypoxia. Although the serum levels of VEGF were not significantly different between groups, the mRNA transcripts for VEGF, VEGF-R2, and neuronal nitric oxide synthase were significantly greater for the BFR condition at 4 and 24 hours postexercise. Based on these results, future investigations might investigate the link between acute angiogenic stimulating factors and longitudinal improvements in measures of localized muscular endurance.

Takarada et al. (90) found concomitant increases in muscle CSA (12.3%) and knee extensor dynamic endurance after BFR training (~200 mm Hg; 33-mm cuff width) vs. an identical work-matched protocol without BFR. Knee extensor dynamic endurance was assessed >50 repeated concentric contractions as the percentage decrease of mechanical work and the average value of peak torque during the last 10 contractions vs. the initial 10 contractions. The training protocol involved 4 sets of bilateral knee extensions to failure at 50% of 1RM and was conducted twice weekly for 8 weeks. The authors attributed the results to peripherally mediated adaptations (i.e., increased oxidative energy metabolism and acid-buffering capacity) rather than centrally mediated adaptations (i.e., neural drive).

Kacin and Strazer (38) used a protocol that involved 4 sets of unilateral leg extensions (15% of MVC) to failure. Four sessions were performed weekly for 4 weeks with BFR applied to 1 leg at 230 mm Hg (I-Leg) and an identical work-matched protocol to the contralateral leg (C-Leg). During the postintervention, each leg (irrespective of training condition) was evaluated for localized muscular endurance under occluded (230 mm Hg) and nonoccluded conditions via dynamic knee extensions to failure at 15% MVC. It was determined that occluded and unoccluded localized muscular endurance increased but to a greater extent for the I-Leg 63 and 27% vs. the C-Leg 36 and 11%,

respectively. These studies (38,90) suggest that the addition of BFR during resistance training can promote superior increases in localized muscular endurance and might promote a crosseducation effect on contralateral muscle groups not trained via BFR.

Muscle Fiber Recruitment

Activation of FT fibers is crucial in achieving a significant hypertrophic response. Recruitment of muscle fibers typically follows the “size principle” in which larger motor units containing FT fibers are progressively recruited for greater muscular torque as the training load increases (34). Yet, Moritani (68) demonstrated greater recruitment of FT fibers during 4 minutes (2-second contractions with 2-second rest intervals) of grip strength exercise at 20% MVC under conditions of BFR (200 mm Hg; cuff width not reported) compared with the same exercise protocol performed without BFR on the contralateral limb. The authors observed increases in motor unit firing rate and spike amplitude consistent with greater recruitment of FT motor units. These results may be attributed to muscular fatigue, which may alter motor unit activation and the orderly recruitment of muscle fibers as dictated by the size principle (80). Several other studies measuring muscle activation via electromyography (EMG) during unfatigued contractions demonstrated significantly greater responses with the application of BFR (91,100,101).

Conversely, Wernbom et al. (97) in examining 3 sets of low-intensity (30% of 1RM) unilateral knee extensions with BFR (100 mm Hg; 135-mm cuff width) and without BFR, found similar EMG activity patterns, with the exception that without BFR, set 3 demonstrated greater EMG activity during the eccentric phase, when all sets were performed to repetition failure. Similarly, Kacin and Strazer (38) evaluated vastus medialis and rectus femoris EMG activity during dynamic knee extensions performed to repetition failure under 2 different conditions: (a) (Con) 15% of MVC without BFR, (b) (Isch) 15% of MVC with BFR at 230 mm Hg. The authors found similar increases in EMG amplitude during both (Isch and Con) testing conditions. Furthermore, when tested again after a 4-week training period (4 sets; 4 sessions weekly; 15% MVC; unilateral knee extension), activation of the rectus femoris was significantly (~45%) reduced with a concomitant tendency for reduced vastus medialis activation, for the occluded vs. the nonoccluded condition. These results might indicate greater sensory feedback or perception of exertion (50) during BFR that inhibits motor drive and subsequent levels of muscle activity.

Suga et al. (85) compared 3 sets of unilateral plantar flexor contractions (20% of 1RM; 30 repetitions each set; 1-minute rest intervals between sets) with BFR (1.3× resting systolic pressure; 18.5-cm cuff width) vs. without BFR (65% of 1RM) and observed a similar portion of subjects during each condition displaying split inorganic phosphate (Pi) peaks (representing FT fiber recruitment) via ³¹P-magnetic resonance

spectroscopy. Fujita et al. (26) found that resistance exercise with BFR, compared with a “work-matched” protocol without BFR, demonstrated increased S6 kinase1 (S6K1) phosphorylation, which primarily occurs in type 2 muscle fibers (40), indirectly linking BFR to increased recruitment of FT fibers. Moore et al. (67) demonstrated that partial vascular occlusion resulted in neuromuscular modulation via depressed resting twitch torque (21%) and enhanced post-activation potentiation (51%) likely through increased calcium responsiveness. Moreover, Moore et al. (67) found that voluntary motor unit activation is not enhanced after 8 weeks of BFR training, as did Kubo et al. (45).

Considering the totality of current research, there is emerging evidence that BFR can enhance recruitment of higher threshold motor units. Given that fibers must be recruited to stimulate adaptations, and given that FT fibers have a substantially greater hypertrophic potential compared with slow twitch fibers, this phenomenon would seem to be associated with at least some of the increases in muscle strength and hypertrophy associated with BFR training. However, conflicting research on the topic suggests that this is not the only mechanism responsible for such adaptations, and that other factors likely also play a role. Further study is needed to clarify the precise relationship between BFR and muscle recruitment and to elucidate its associated implications.

METABOLIC RESPONSES

Metabolic stress (i.e., as manifested in decreased adenosine triphosphate [ATP], depletion of phosphocreatine [PCr], increased Pi, increased adenosine diphosphate/ATP ratio, increased adenosine monophosphate [AMP] production, decreased intramuscular pH, and accumulation of lactate) has been suggested to be a key stimulator of physiological adaptations (31,43). Numerous studies have found that the ischemic (88) and hypoxic (92) intramuscular environment associated with BFR protocols induces a greater rate of ATP hydrolysis, exaggerated PCr depletion (85) decreased pH (84,85), and an increased lactate response (26,74,76,88,89). Suga et al. (84) found greater metabolic stress (i.e., PCr, Pi, and deprotonated phosphate) via ³¹P-magnetic resonance spectroscopy, during low-intensity exercise (20% of 1RM) with BFR (varying pressure; 18.5-cm cuff width) vs. low-intensity (20% of 1RM) without BFR. However, the degree of metabolic stress was significantly less vs. a higher intensity protocol without BFR (65% of 1RM).

However, it is also important to note that Suga et al. (84) used a single set of repetitions to exhaustion. In separate research, Suga et al. (85) examined the acute effects of multiple sets on intramuscular metabolic stress during 2 separate low-intensity plantar flexion exercise bouts (20% of 1RM; 3 sets of 30 repetitions; 1-minute rest intervals between) under 2 distinct BFR bouts (intermittent—pressure released during rest intervals between sets; continuous—pressure maintained throughout exercise and released after the final set); and

a high-intensity bout (65% of 1RM; 3 sets of 30 repetitions; 1-minute rest intervals between sets) and a low-intensity bout (20% of 1RM; 3 sets of 30 repetitions per set; 1-minute rest intervals between sets), both without BFR. It was found that the “intermittent” bout with BFR elicited a nonsignificant trend toward greater metabolic stress compared with the low-intensity bout without BFR. Furthermore, only the “continuous” bout with BFR elicited similar metabolic stress to the high-intensity bout without BFR.

When the rate of ATP hydrolysis (as dictated by exercise intensity) is greater than the rate of ATP production via mitochondrial respiration, the accumulation of protons (H^+) increases intramuscular acidity; the lactate dehydrogenase reaction serves as an avenue for proton consumption in the conversion of pyruvate to lactate. Lactate is transported via the bloodstream to the liver for conversion to glucose. Therefore, the blood lactate concentration serves as a good indirect measure of metabolic demand (78). High intramuscular proton concentrations can inhibit Ca^{2+} release from the sarcoplasmic reticulum, disrupting excitation-contraction coupling of myofilaments, thereby reducing tension development as manifested in peripheral muscular fatigue (23).

The metabolic stress associated with long-term BFR training led to a significant increase in glycogen stores (10). Furthermore, Burgomaster et al. (10) also noted a decrease in the resting ATP concentration after long-term BFR training. The authors hypothesized that the metabolic adaptations accompanying BFR training might be mediated through alterations in glucose transport (GLUT-4 translocation) and glycogen resynthesis (glycogen synthase activity). Research has indicated that hypoxia increases GLUT-4 translocation to the sarcolemma, stimulating muscle glucose uptake (14). Furthermore, evidence suggests that hypoxia-mediated and contraction-mediated glucose uptake can operate through independent mechanisms (24). The increased duration of metabolic stress unique to BFR exercise likely facilitates many other physiological responses and adaptations.

ENDOCRINE RESPONSES

Proton accumulation and the ensuing metabolic acidosis (i.e., decreased pH) are associated with growth hormone (GH) and gonadotropin release (29,42,59,89,99). Previous research indicated that low-threshold afferents (type 1 and 2) stimulated release of bioassayable (biologically active) forms of GH, whereas immunoassayable GH was unaffected (30). However, Pierce et al. (74) found an increase in immunoassayable GH after resistance exercise with BFR that may rule out type 1 and 2 afferent nerve contribution to the GH response after BFR training. It was hypothesized that the increased GH response was likely because of metabolite accumulation and the subsequent metaboreflex via muscle chemoreceptor stimulation of type 3 and 4 afferents (42,74). Upon binding to the membrane-bound receptor, GH initiates janus kinase 2 signaling, which activates phosphatidylinositol-3 kinase,

an upstream regulator of the protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway (75).

It is somewhat controversial whether the systemic GH response to metabolic acidosis affects strength and hypertrophy adaptations. Systemic elevations in GH might not reflect the degree of receptor interaction and subsequent downstream signaling for muscle growth. However, Kraemer et al. (43) demonstrated that a “hypertrophy” type regimen, consisting of 3 sets of 8 exercises, performed with a 10RM load, and 1-minute rest interval between sets produced greater acute increases in GH vs. a “strength” type regimen, consisting of 5 sets of 5 exercises, performed with a 5RM load, and a 3-minute rest interval between sets. McCall et al. (65) used a similar “hypertrophy” type regimen in a 12-week training study that demonstrated significant correlations between acute GH increases and the relative degree of type 1 ($r = 0.74$) and type 2 ($r = 0.71$) muscle fiber hypertrophy in the biceps brachii. Furthermore, Goto et al. (32) reported that a “hypertrophy” type regimen that elicited greater acute GH release was associated with greater longitudinal increases in quadriceps CSA vs. a “strength” type regimen.

Studies that have compared resistance exercise protocols with or without BFR have demonstrated a significantly greater systemic GH release subsequent to the BFR protocol (26,74,76,89). Hence, a key mechanism underlying the BFR induced hypertrophy might be the increased duration of metabolic acidosis that evokes systemic GH release. Takarada et al. (89) reported a plasma GH increase of 290-fold with similar responses in lactate and norepinephrine after 5 sets of bilateral leg extension with low intensity (~20% of 1RM to failure; 30-second rest intervals between sets) when combined with BFR (~215 mm Hg; 33-mm cuff width) in young male participants. This is approximately 1.7 \times larger than what would be expected based on previous research on traditional resistance exercise (43). Many other studies also reported increases in GH (3,23,65,67,81) subsequent to BFR exercise.

To test the metabolic accumulation hypothesis, Inagaki et al. (36) examined electromyostimulation (EMS) induced involuntary unilateral knee extensions (20 Hz; 400 microseconds; 3- to 1-second ratio; 40-second duration for the first and second sets, 60 seconds for the third set) with and without BFR (150 mm Hg; 20.5-cm cuff width), and found that serum 22-kD immunoreactive GH increased only during the BFR condition. Inagaki et al. (36) also found that the total production of lactate was similar between conditions. However, during the BFR condition, the time course of the lactate response indicated that metabolites were retained and had accumulated in the working muscle. This finding was similar to Reeves et al. (76), who compared low-intensity (30% of 1RM) elbow flexion and plantar flexion with BFR (cuff pressure set at 20 mm Hg below resting systolic pressure for upper body and 40 mm Hg above upper body occlusive pressure; cuff width not reported) to moderate intensity without BFR (70% of 1RM)

and found equivalent lactate responses, albeit a larger GH response in the low intensity with BFR condition. This would seem to indicate that lactate (and the associated metabolic acidosis) is not the only modulator of the GH response to BFR exercise.

Catecholamines (e.g., epinephrine, norepinephrine) act as powerful modulators of numerous physiological responses for sustaining exercise (64). Research has demonstrated an increase in the norepinephrine concentration after BFR exercise (60,89), yet during EMS stimulated involuntary contraction with BFR, the increase was substantially less, possibly indicating that norepinephrine secretion depends on centrally mediated voluntary exertion (36).

Loenneke et al. (57) discussed the hypertrophic role of catecholamines through β_2 adrenoceptor signaling—the most prominent adrenoceptor found in skeletal muscle tissue. The binding of catecholamines to β_2 adrenoceptors initiates the G-protein-linked activation of the cyclic AMP secondary messenger, and then activation of protein kinase A dependent (e.g., inhibition of calcium-dependent proteolysis) and independent mechanisms (activation of the phosphatidylinositol-3-kinase pathway). The norepinephrine and muscle cell swelling responses to BFR might attenuate muscle atrophy in the absence of exercise. When BFR is combined with exercise, the norepinephrine response is amplified, but other mechanisms (muscle activity, hormones, metabolites) might play a more prominent role for strength and hypertrophic adaptations.

Circulating GH is known to stimulate synthesis and secretion of insulin-like growth factor 1 (IGF-1). Abe et al. (5) reported an increased IGF-1 response to low-intensity (20% of 1RM) resistance training with BFR (240 mm Hg; cuff width not reported). The control group in this study performed a protocol with the same intensity and volume but did not demonstrate a similar response. This increased IGF-1 response to BFR resistance exercise was also observed by Takano et al. (88); moreover, BFR in conjunction with walking did not increase IGF-1 (3).

A recent review by Loenneke et al. (56) indicated minimal acute and chronic testosterone changes subsequent to BFR plus exercise. Studies that examined the total testosterone (3,26,76) and free testosterone responses (3,76) to BFR have indicated no significant increases. However, the lack of testosterone response may have been attributable to the low exertion type of exercise mode (Abe et al. [3]—walking 50 $\text{m} \cdot \text{min}^{-1}$); insufficient exercise volume (Reeves et al. [76]: 3 sets elbow flexion and plantar flexion at 30% of 1RM; Fujita et al. [26]: 4 sets leg extensions at 20% of 1RM); or limited total muscle mass involvement during an exercise session (biceps brachii, gastrocnemius, quadriceps).

The stress associated with resistance exercise is known to increase cortisol concentrations. Fujita et al. (26) compared 4 sets (30, 15, 15, 15 repetitions) of bilateral knee extensions at low intensity (20% of 1RM) with and without BFR (200 mm Hg; cuff width not reported). The authors found an elevated cortisol concentration after the BFR protocol compared

with a work-matched control session at 10, 20, 30, 40, 50, and 60 minutes postexercise. The greater cortisol concentration after the BFR session in this study (26) was likely indicative of a greater stress response; this is evident by the fact that cortisol levels had returned to baseline at approximately 1 hour postexercise.

Overall, BFR exercise has demonstrated similar acute systemic hormonal responses as traditional resistance exercise without BFR. Some of the hormonal responses were larger (1,76,88,89), or at least comparable (3,26,76) with traditional high-intensity resistance exercise with considerably less mechanical stress.

MUSCLE DAMAGE RESPONSE

Traditional non-BFR higher intensity resistance exercise is associated with acutely elevated myoglobin, LP, creatine kinase (CK), and cytokines (mainly interleukin-6 [IL-6], transforming growth factor- β [TGF- β], and tumor necrosis factor- α [TNF- α]). Research on muscle damage after BFR in conjunction with resistance exercise is not yet conclusive. Takarada et al. (89) examined the effect of BFR exercise at 20% of 1RM on concentrations of IL-6, CK, and LP. The authors reported a gradual increase in IL-6 concentration to approximately 1 $\text{pg} \cdot \text{ml}^{-1}$ within 90 minutes postexercise with no significant changes in the concentrations of CK and LP.

Fujita et al. (26) examined low-intensity (4 sets; 30 repetitions first set, followed by 3 sets of 15 repetitions at 20% of 1RM; 30-second rest intervals between sets) bilateral knee extension with and without BFR (200 mm Hg; cuff width not reported) on acute markers of muscle damage (e.g., IL-6, CK, and myoglobin) before, immediately after, 24 hours after, and 48 hours postexercise. Results indicated no significant changes in IL-6, CK, and myoglobin for either condition. Furthermore, Abe et al. (3) found no significant changes in the resting plasma activity of CK and myoglobin from baseline to post, after a 3-week (twice daily; 6 $\text{d} \cdot \text{wk}^{-1}$) continuous BFR (200 mm Hg; 50-mm cuff width) walk training intervention; each session involved 5 bouts; 2-minute duration per bout; walking speed on a treadmill of 50 $\text{m} \cdot \text{min}^{-1}$; and 1-minute rest intervals between bouts.

Conversely, Wernbom et al. (98) examined max force production after 5 sets of knee extensions to repetition failure (30% of 1RM) with BFR (90–100 mm Hg; 135-mm cuff width) and found significant decrements in MVC (via neuromuscular electrical stimulation) that remained depressed for the succeeding 48 hours. However, these results were obtained during BFR. After the cuff pressure was released, there was no significant difference between groups. Similar results were reported by Umbel et al. (95) in comparing 3 sets of the unilateral knee extension with and without BFR (cuff pressure set to 30% above resting systolic pressure; 6-cm cuff width) and found significantly depressed MVC at 24 hours postexercise for the BFR condition. Wernbom et al. (98) compared 5 sets with repetition failure of the

unilateral knee extension with BFR vs. a work-matched contralateral protocol, and determined that the BFR condition resulted in greater plasma protein tetranectin levels (a marker for sarcolemmal permeability) after 24 hours, suggesting indirectly that greater muscle damage was evident for the BFR condition vs. the non-BFR condition. It should be noted that the work-matched free flow condition also displayed an elevated tetranectin percentage. More research is needed to determine the efficacy of tetranectin staining in quantification of muscle damage.

Little is known about the anti/inflammatory response and other markers of muscle damage for BFR resistance exercise at intensities >20–30% of 1RM. Traditional non-BFR higher intensity exercise is associated with muscle damage and inflammation. The muscle damage and inflammatory process caused at higher intensities can attenuate recovery from exercise. Because of the evidence of less muscle damage associated with BFR at low intensities, researchers have experimented with an increased frequency of BFR resistance exercise to as much as twice daily for 6 d·wk⁻¹ (1,20), yielding a significant hypertrophic response. However, numerous studies report BFR exercise results in delayed-onset muscular soreness (DOMS [95,96]); it should be noted however, that Umbel et al. (95) has subjects retrospectively rate DOMS, which is not the typical method of measurement. Moreover, DOMS is not necessarily well correlated to various markers of muscle damage including maximal isometric strength, range of motion, upper arm circumference, and plasma CK levels (71), making it a poor gauge of both the presence and magnitude of tissue trauma. Further research is needed on this issue particularly with regard to the training status of participants undergoing BFR exercise. For clinical populations, more frequent use of BFR training might be possible because of potentially lower exertion levels.

CELLULAR AND MOLECULAR SIGNALING

Fundamental to skeletal muscle hypertrophy is the stimulation of muscle protein synthesis, crucial to which is the protein kinase B/mammalian target of rapamycin (Akt/mTOR) signaling pathway via phosphorylation action on the 70-kDa ribosomal protein S6K/ribosomal proteins (rps) and eukaryotic initiation factor 4E binding protein (4E-BP)/translation initiation factors (9). Hypoxia is known to cause reversible hypophosphorylation of mTOR and downstream effectors 4E-BP1, p70 S6K, rpS6, and eukaryotic initiation factor 4 G, inhibiting cellular translation (8). The principal finding of Fujita et al. (26) was that BFR resistance exercise resulted in increased ribosomal S6K1 phosphorylation concurrent with decreased phosphorylation of eukaryotic translation elongation factor 2 resulting in a 46% increase in muscle protein synthesis compared with a control session. Fry et al. (25) found an increase in mTOR complex 1 and S6K1 phosphorylation, and ribosomal protein S6 resulting in a 56% increase in muscle protein synthesis vs. a control session when

researching the effects of BRF training in older men approximately 70 years old.

Drummond et al. (19) examined a variety of mRNA expression factors associated with tissue growth and remodeling during low-intensity resistance exercise with or without BFR. The authors examined specific factors hypothesized to potentially modulate the acute response to resistance exercise, both anabolic and catabolic in nature. The training protocol involved 4 sets of the leg extension (e.g., repetition numbers per set were 30, 15, 15, 15, respectively) at an intensity of 20% of 1RM, with 30-second rest intervals between sets and the application of approximately 200-mm Hg external pressure (cuff width not reported). Three weeks later, a second, work-matched session was performed without application of external pressure.

Drummond et al. (19) found significant upregulation in the expression of numerous mRNA transcription factors (cyclin D1, IGF-1R, MGF, myogenin, mTOR, S6K1, and MAFbx) from baseline to 3 hours post in both conditions. Other variables demonstrated significant increases (HIF-1 α , p21, MyoD, and MuRF) or decreases (REDD-1 and myostatin). However, there was no significant difference in the expression of mRNA for any variable at any point between the 2 conditions (i.e., BFR vs. non-BFR). Interestingly, HIF-1 α mRNA expression did not correlate with a corresponding increase in REDD-1 mRNA expression. Therefore, HIF-1 α expression does not appear to be synonymous with REDD-1 activity. Other research has found that HIF-1 α expression is important to oxygen homeostasis, cell survival and is known to increase under hypoxic conditions, modulating activity of VEGF, glucose transporters, glycolytic enzymes, inducible NOS, and IGF2 (82). Although Drummond et al. (19) elucidated a potential contribution of both HIF-1 α and REDD-1 to skeletal muscular hypertrophy during low-intensity resistance exercise; the altered hypertrophic response associated with BFR remains unresolved.

Laurentino et al. (49) found similar and significant decreases in the expression of myostatin (with concomitant hypertrophy) after 8 weeks of knee extension training in a low intensity with BFR (~95-mm Hg cuff pressure; 175-mm cuff width) training group and a high intensity without BFR training group; the decreases in myostatin were 45 and 41%, respectively. However, an acute study conducted by Drummond et al. (19) indicated no differences in myostatin gene expression between a BFR protocol at 20% of 1RM and a similar intensity protocol without BFR 3 hours postexercise. These results were consistent with acute results reported by Manini et al. (63) for myostatin expression in comparing similar protocols as Drummond et al. (19). However, Manini et al. (63) reported other significant acute responses such as decreases in various proteolytic transcription factors (FOXO3A, Atrogin-1, and MuRF-1) 8 hours postexercise in favor of the BFR plus resistance exercise group. In comparing the acute vs. longitudinal findings, the timing of measurements seems to be a key issue; as in the longitudinal study (49), changes in hypertrophy

stimulating variables (e.g., reduction in myostatin expression) may take several weeks to be fully evident.

Heat shock proteins (HSPs) are thought to play a role in modulating the effects of oxidative and heat stress maintaining cellular homeostasis and aiding in protein assembly and membrane translocation. Numerous HSPs have been identified, each of which are named according to their molecular mass in kilodaltons (i.e., HSP27, HSP60, HSP70, and HSP72), and their transcription can be induced by a variety of factors including ROS, hypoxia, acidosis, and ischemia/reperfusion (44). Given that increases in HSP-72 correlated with a significant increase in muscle hypertrophy, Ishii et al. (37) hypothesized a possible casual role in post-exercise muscular development via BFR training. Conversely, Fry et al. (25) found no differences in total protein content of HSP70 after BFR exercise at 20% 1RM in elderly men. This suggests the possibility that different HSPs may have varying effects with respect to muscular adaptations.

SAFETY ISSUES

Apart from the potential benefits of BFR training, one must always consider potential negative outcomes (62). It is well known that prolonged ischemia can cause necrosis of muscle tissue. Furthermore, a major concern with BFR training is the potential for thrombus formation (62) because of the pooling of blood in the extremities. However, Madarame et al. (60) found that 4 sets of leg press with continuous BFR (150–160 mm Hg; cuff width not reported) at 30% of 1RM with 30-second rest intervals between sets did not increase prothrombin fragments 1 + 2 or thrombin-anti-thrombin III complex (markers of thrombin generation), nor did BFR exercise increase D-dimer or fibrin degradation products (markers of intravascular clot formation).

Nakajima et al. (69) surveyed >100 facilities that use BFR exercise to determine the incidence of adverse events in the field. The authors reported that nearly 13,000 individuals (age range; ≤ 20 to ≥ 80), with a variety of different physical conditions used BFR exercise. The incidence of side effects was as follows: cerebral anemia (0.277%), venous thrombus (0.055%), pulmonary embolism (0.008%), rhabdomyolysis (0.008), and deterioration of ischemic heart disease (0.016%). However, BFR exercise resulted in the following incidence of temporary side effects, including; subcutaneous hemorrhage (13.1%), numbness (1.297%), and cold feeling (0.127%); likely because of compression to musculature and peripheral nerves. Research examining the safety of BFR exercise and training has thus far concluded that BFR exercise is a safe and novel method for training athletes, healthy persons (15), and potentially those individuals with varying comorbidities (69).

PRACTICAL APPLICATIONS

The American College of Sports Medicine recommended approximately 60–100% of 1RM as the resistive load necessary to induced adaptational characteristics such as muscular

strength, hypertrophy, and to some extent, absolute muscular endurance (7). However, resistance training in combination with BFR may induce similar expression of adaptational characteristics as high-intensity resistance training, but at considerably lower intensities (20–50% of 1RM). The application of BFR exercise may be best suited for populations that cannot tolerate the large mechanical loads imposed during high-intensity resistance training. Unfortunately, current research has yet to fully determine the efficacy of BFR in conjunction with resistance exercise in individuals with varying morbidities. Therefore, prescriptive exercise variables for clinical populations are not yet definable, but in healthy populations, BFR exercise may provide an alternative means of obtaining a hypertrophic effect in a relatively short time period.

Application of external pressure to the proximal portion of the lower extremity (i.e., inguinal crease) or upper extremity (i.e., distal portion of deltoid) can be obtained via pressurized cuff or elastic knee wraps (53). It should be emphasized that the strength and hypertrophic adaptations may take place at muscles that are proximal or distal to the occlusion site (4). For example, bench press training with the application of BFR has elicited hypertrophy in both the pectoralis major (proximal to the occlusion site) and the triceps brachii (distal to the occlusion site) (102).

The external pressure applied should be sufficient to maintain arterial inflow while occluding venous outflow of blood distal to the occlusion site; with the external pressure applied, the pulse should still be palpable distal to the occlusion site. If a pressurized cuff is being used to control external pressure, consideration should also be given to the width of the cuff as it has been demonstrated that as cuff width increases, the pressure requirements to achieve a given percentage of restricted blood flow decreases (17,52). Furthermore, Loenneke et al. (52) has emphasized that thigh circumference is a key variable in choosing appropriate lower-body cuff pressures. When using pressurized cuffs, the cuffs should be positioned with a slightly loose fit before inflation to prevent the material (containing the pneumatic bag) from becoming occlusive itself.

The BFR resistance exercise might be performed 2–3 times weekly for the same muscles or muscle groups. However, higher frequencies (up to twice daily) might be instituted depending on individual training status and goals; volume or duration of BFR exercise; and exercise modality (5,72). For example, slow walking in conjunction with BFR might be performed twice daily (72), whereas exhaustive bilateral knee extensions might be performed 2 or 3 times weekly (55).

One approach for resistance exercise is to group BFR sets into “blocks” in which pressure is constant throughout the duration of each block to closely monitor “time under occlusion” with release of pressure between blocks to allow for reperfusion. One block may involve 2–4, low-intensity (30–50% of 1RM) sets performed until repetition failure with short rest intervals between sets (30–60 seconds) and with

a traditional resistance exercise cadence (1- to 2-second concentric phase; 1- to 2-second eccentric phase). The total “time under occlusion” for one block (2–4 sets continuous occlusion) might be approximately 5 minutes. One to 3 blocks might be performed per exercise, with 5 minutes between blocks without the application of BFR to allow for reperfusion and recovery (unpublished observations).

Continuous BFR between resistance exercise sets attenuates the natural recovery process that normally takes place during the interset rest interval, thus accentuating metabolite accumulation. Therefore, repetitions are typically maintained over consecutive sets by decreasing the load intensity between consecutive sets within a block. Furthermore, alternating agonist and antagonist movements with continuous BFR can be used as well to increase the total volume efficiently by alternating opposing muscle groups.

REFERENCES

- Abe, T, Fujita, S, Nakajima, T, Sakamaki, M, Ozaki, H, Ogasawara, R, Sugaya, M, Kudo, M, Kurano, M, Yasuda, T, Sato, Y, Ohshima, H, Mukai, C, and Ishii, N. Effects of low-intensity cycle training with restricted leg blood flow on thigh muscle volume and VO_{2max} in young men. *J Sports Sci Med* 9: 452–458, 2010.
- Abe, T, Kearns, CF, Fujita, S, Sakamaki, M, Sato, Y, and Brechue, WF. Skeletal muscle size and strength are increased following walk training with restricted leg muscle blood flow: Implications for training duration and frequency. *Int J KAATSU Training Res* 5: 9–15, 2009.
- Abe, T, Kearns, CF, and Sato, Y. Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J Appl Physiol* 100: 1460–1466, 2006.
- Abe, T, Loenneke, JP, Fahs, CA, Rossow, LM, Thiebaut, RS, and Bembem, MG. Exercise intensity and muscle hypertrophy in blood flow-restricted limbs and non-restricted muscles: A brief review. *Clin Physiol Funct Imaging* 32: 247–252, 2012.
- Abe, T, Sato, Y, Inoue, K, Midorikawa, T, Yasuda, T, and Kearns, CF, et al. Skeletal muscle size and circulating IGF-1 are increased after two weeks of twice daily KAATSU resistance training. *Int J Kaatsu Training Res* 1: 6–12, 2005.
- Alessio, HM, Hagerman, AE, Fulkerson, BK, Ambrose, J, Rice, RE, and Wiley, RL. Generation of reactive oxygen species after exhaustive aerobic and isometric exercise. *Med Sci Sports Exerc* 32: 1576–1581, 2000.
- American College of Sports Medicine. Progression Models in resistance training for healthy adults. *Med Sci Sports Exerc* 41: 687–708, 2009.
- Arsham, A, Howell, J, and Simon, M. A novel hypoxia-inducible factor-independent hypoxic response regulating mammalian target of rapamycin and its targets. *J Biol Chem* 278: 29655–29660, 2003.
- Bodine, SC, Stitt, TN, Gonzales, M, Kline, WO, Stover, GL, Bauerlein, R, Zlotchenko, E, Scrimgeour, A, Lawrence, JC, Glass, DJ, and Yancopoulos, GD. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol* 3: 1014–1019, 2001.
- Burgomaster, K, Moore, D, Schofield, L, Phillips, S, Sale, D, and Gibala, M. Resistance training with vascular occlusion: Metabolic adaptations in human muscle. *Med Sci Sports Exerc* 35: 1203–1208, 2003.
- Cacchiuto, MA, Trinh, L, Lumpkin, JA, and Rao, G. Hyperoxia induces DNA damage in mammalian cells. *Free Radic Biol Med* 14: 267–276, 1993.
- Campos, GE, Luecke, TJ, Wendeln, HK, Toma, K, Hagerman, FC, Murray, TF, Ragg, KE, Ratamess, NA, Kraemer, WJ, and Staron, RS. Muscular adaptations in response to three different resistance-training regimens: Specificity of repetition maximum training zones. *Eur J Appl Physiol* 88: 50–60, 2002.
- Carruthers, NJ and Stemmer, PM. Methionine oxidation in the calmodulin-binding domain of calcineurin disrupts calmodulin binding and calcineurin activation. *Biochemistry* 47: 3085–3095, 2008.
- Cartee, GD, Douen, AG, Ramlal, T, Klip, A, and Holloszy, JO. Stimulation of glucose transport in skeletal muscle by hypoxia. *J Appl Physiol* 70: 1593–1600, 1991.
- Clark, BC, Manini, TM, Hoffman, RL, Williams, PS, Guiler, MK, Knutson, MJ, McGlynn, ML, and Kushnick, MR. Relative safety of 4 weeks of blood flow-restricted resistance exercise in young, healthy adults. *Scand J Med Sci Sports* 21: 653–662, 2011.
- Credeur, DP, Hollis, BC, and Welsch, MA. Effects of handgrip training with venous restriction on brachial artery vasodilation. *Med Sci Sports Exerc* 42: 1296–1302, 2010.
- Crenshaw, A, Hargens, A, Gershuni, D, and Rydevik, B. Wide tourniquet cuffs more effective at lower inflation pressures. *Acta Orthop Scand* 59: 447–451, 1988.
- Dangott, B, Schultz, E, and Mozdzia, PE. Dietary creatine monohydrate supplementation increases satellite cell mitotic activity during compensatory hypertrophy. *Int J Sports Med* 21: 13–16, 2000.
- Drummond, M, Fujita, S, Abe, T, Dreyer, H, Volpi, E, and Rasmussen, B. Muscle gene expression following resistance exercise and blood flow restriction. *Med Sci Sports Exerc* 40: 691–698, 2008.
- Dunn, SE, Chin, ER, and Michel, RN. Matching of calcineurin activity to upstream effectors is critical for skeletal muscle fiber growth. *J Cell Biol* 151: 663–672, 2000.
- Fahs, CA, Rossow, LM, Loenneke, JP, Thiebaut, RS, Kim, D, Bembem, DA, and Bembem, MG. Effect of different types of lower body resistance training on arterial compliance and calf blood flow. *Clin Physiol Funct Imaging* 32: 45–51, 2012.
- Fahs, CA, Rossow, LM, Seo, DI, Loenneke, JP, Sherk, VD, Kim, E, Bembem, DA, and Bembem, MG. Effect of different types of resistance exercise on arterial compliance and calf blood flow. *Eur J Appl Physiol* 111: 2969–2975, 2011.
- Favero, TG, Zable, AC, Colter, D, and Abramson, JJ. Lactate inhibits Ca^{2+} -activated Ca^{2+} -channel activity from skeletal muscle sarcoplasmic reticulum. *J Appl Physiol* 82: 447–452, 1997.
- Fluckey, JD, Ploug, T, and Galbo, H. Mechanisms associated with hypoxia- and contraction-mediated glucose transport in muscle are fibre-dependent. *Acta Physiol Scand* 167: 83–87, 1999.
- Fry, CS, Glynn, EL, Drummond, MJ, Timmermann, KL, Fujita, S, Abe, T, Dhanani, S, Volpi, E, and Rasmussen, BB. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *J Appl Physiol* 108: 1199–1209, 2010.
- Fujita, S, Abe, T, Drummond, M, Cadenas, J, Dreyer, H, Sato, Y, Volpi, E, and Rasmussen, BB. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* 103: 903–910, 2007.
- Fujita, T, Brechue, W, Kurita, K, Sato, Y, and Abe, T. Increased muscle volume and strength following six days of low-intensity resistance training with restricted muscle blood flow. *Int J KAATSU Res* 4: 1–8, 2008.
- Goldfarb, AH, Garten, RS, Chee, PD, Cho, C, Reeves, GV, Hollander, DB, Thomas, C, Aboudehen, KS, Francois, M, and Kraemer, RR. Resistance exercise effects on blood glutathione status and plasma protein carbonyls: Influence of partial vascular occlusion. *Eur J Appl Physiol* 104: 813–819, 2008.
- Gordon, S, Kraemer, W, Vos, N, Lynch, J, and Knuttgen, H. Effect of acid-base balance on growth hormone response to acute high intensity cycle exercise. *J Appl Physiol* 76: 821–829, 1994.

30. Gosselink, KL, Grindeland, RE, Roy, RR, Zhong, H, Bigbee, AJ, Grossman, EJ, and Edgerton, VR. Skeletal muscle afferent regulation of bioassayable growth hormone in rat pituitary. *J Appl Physiol* 84: 1425–1430, 1998.
31. Goto, K, Kizuka, T, and Takamatsu, K. The impact of metabolic stress on hormonal responses and muscular adaptations. *Med Sci Sports Exerc* 37: 955–963, 2005.
32. Goto, K, Nagasawa, M, Yanagisawa, O, Kizuka, T, Ishii, N, and Takamatsu, K. Muscular adaptations to combinations of high and low intensity resistance exercises. *J Strength Cond Res* 18: 730–737, 2004.
33. Gundermann, DM, Fry, CS, Dickinson, JM, Walker, DK, Timmerman, KL, Drummond, MJ, Volpi, E, and Rasmussen, BB. Reactive hyperemia is not responsible for stimulating muscle protein synthesis following blood flow restriction exercise. *J Appl Physiol* 112: 1520–1528, 2012.
34. Henneman, E, Somjen, G, and Carpenter, DO. Functional significance of cell size in spinal motoneurons. *J Neurophysiol* 28: 560–580, 1965.
35. Hornberger, TA, McLoughlin, TJ, Leszczynski, JK, Armstrong, DD, Jameson, RR, Bowen, PE, Hwang, ES, Hou, H, Moustafa, ME, Carlson, BA, Hatfield, DL, Diamond, AM, and Esser, KA. Selenoprotein-deficient transgenic mice exhibit enhanced exercise-induced muscle growth. *J Nutr* 133: 3091–3097, 2003.
36. Inagaki, Y, Madarame, H, Neya, M, and Ishii, N. Increase in serum growth hormone induced by electrical stimulation of muscle combined with blood flow restriction. *Eur J Appl Physiol* 111: 2715–2721, 2011.
37. Ishii, N, Madarame, H, Odagiri, K, Naganuma, M, and Shinoda, K. Circuit training without external load induces hypertrophy in lower-limb muscles when combined with moderate venous occlusion. *Int J KAATSU Training Res* 1: 24–28, 2005.
38. Kacin, A and Strazer, K. Frequent low-load ischemic resistance exercise to failure enhances muscle oxygen delivery and endurance capacity. *Scand J Med Sci Sports* 21: 231–241, 2011.
39. Kim, SJ, Sherk, VD, Bembem, MG, and Bembem, DA. Effects of short-term, low-intensity resistance training with vascular restriction on arterial compliance in untrained young men. *Int J KAATSU Training Res* 5: 1–8, 2009.
40. Koopman, R, Zorenc, AH, Gransier, RJ, Cameron-Smith, D, and Van Loon, LJ. Increase in S6K1 phosphorylation in human skeletal muscle following resistance exercise occurs mainly in type II muscle fibers. *Am J Physiol Endocrinol Metab* 290: 1245–1252, 2006.
41. Korthuis, RJ, Granger, DN, Townsley, MI, and Taylor, AE. The role of oxygen-derived free radicals in ischemia-induced increases in canine skeletal muscle vascular permeability. *Circ Res* 57: 599–609, 1985.
42. Kraemer, WJ, Gordon, SE, Fleck, SJ, Marchitelli, L, Mello, R, Dziados, J, Friedl, K, Harman, E, Maresh, C, and Fry, AC. Endogenous anabolic hormonal and growth factor response to heavy-resistance exercise in males and females. *Int J Sports Med* 12: 228–235, 1991.
43. Kraemer, WJ, Marchitelli, L, Gordon, SE, Harman, E, Dziados, JE, Mello, R, Fryman, P, McCurry, D, and Fleck, SJ. Hormonal and growth factor responses to heavy resistance exercise protocols. *J Appl Physiol* 69: 1442–1450, 1990.
44. Kregel, KC. Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance. *J Appl Physiol* 92: 2177–2186, 2002.
45. Kubo, K, Komura, T, Ishiguro, N, Tsunoda, N, Sato, Y, Ishii, N, Kanehisa, H, and Fukunaga, T. The effect of low-load resistance training with vascular occlusion on mechanical properties of muscle and tendon. *J Appl Biomech* 22: 112–119, 2006.
46. Lang, F, Busch, GL, Ritter, M, Volkl, H, Waldegger, S, Gulbins, E, and Häussinger, D. Functional significance of cell volume regulatory mechanisms. *Physiol Rev* 78: 247–306, 1998.
47. Larkin, KA, Macneil, RG, Dirain, M, Sandesara, B, Manini, TM, and Buford, TW. Blood flow restriction enhances post-resistance exercise angiogenic gene expression. *Med Sci Sports Exerc* 44: 2077–2083, 2012.
48. Laurentino, GC, Ugrinowitsch, C, Aihara, AY, Fernandes, AR, Parcell, AC, Ricard, M, and Tricoli, V. Effects of strength training and vascular occlusion. *Int J Sports Med* 29: 664–667, 2008.
49. Laurentino, GC, Ugrinowitsch, C, Roschel, H, Aoki, MS, Soares, AG, Neves, M, Aihara, AY, Fernandes, AR, and Tricoli, V. Strength training with blood flow restriction diminishes myostatin gene expression. *Med Sci Sports Exerc* 44: 406–412, 2012.
50. Loenneke, JP, Balapur, A, Thrower, A, and Pujol, TJ. Practical occlusion: Ratings of pain and exertion following two sets to muscular failure. *Int J Sports Med* 32: 181–184, 2011.
51. Loenneke, JP, Fahs, CA, Rossow, LM, Abe, T, and Bembem, MG. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med Hypotheses* 78: 151–154, 2012.
52. Loenneke, JP, Fahs, CA, Rossow, LM, Sherk, VD, Thiebaud, RS, Abe, T, Bembem, DA, and Bembem, MG. Effects of cuff width on arterial occlusion: Implications for blood flow restricted exercise. *Eur J Appl Physiol* 112: 2903–2912, 2011.
53. Loenneke, JP, Kearney, ML, Thrower, A, Collins, S, and Pujol, TJ. The acute response of practical occlusion in the knee extensors. *J Strength Cond Res* 24: 2831–2834, 2010.
54. Loenneke, JP, Wilson, JM, Balapur, A, Thrower, A, Barnes, JT, and Pujol, TJ. Time under tension decreased with blood flow-restricted exercise. *Clin Physiol Funct Imaging* 32: 268–273, 2012.
55. Loenneke, JP, Wilson, JM, Marin, PJ, Zourdos, MC, and Bembem, MG. Low intensity blood flow restriction training: A meta-analysis. *Eur J Appl Physiol* 112: 1849–1859, 2012.
56. Loenneke, JP, Wilson, JM, Pujol, TJ, and Bembem, MG. Acute and chronic testosterone response to blood flow restricted exercise. *Horm Metab Res* 43: 669–673, 2011.
57. Loenneke, JP, Wilson, JM, Thiebaud, RS, Abe, T, Lowery, RP, and Bembem, MG. β_2 Adrenoceptor signaling-induced muscle hypertrophy from blood flow restriction: Is there evidence? *Horm Metab Res* 44: 489–493, 2012.
58. Low, SY, Rennie, MJ, and Taylor, PM. Signaling elements involved in amino acid transport responses to altered muscle cell volume. *FASEB J* 11: 1111–1117, 1997.
59. Luger, A, Watschinger, B, Deuster, P, Svoboda, T, Clodi, M, and Chrousos, GP. Plasma growth hormone and prolactin responses to graded levels of acute exercise and to a lactate infusion. *Neuroendocrinology* 56: 112–117, 1992.
60. Madarame, H, Kurano, M, Takano, H, Iida, H, Sato, Y, Ohshima, H, Abe, T, Ishii, N, Morita, T, and Nakajima, T. Effects of low-intensity resistance exercise with blood flow restriction on coagulation system in healthy subjects. *Clin Physiol Funct Imaging* 30: 210–213, 2010.
61. Madarame, H, Neya, M, Ochi, E, Nakazato, K, Sato, Y, and Ishii, N. Cross-transfer effects of resistance training with blood flow restriction. *Med Sci Sports Exerc* 40: 258–263, 2008.
62. Manini, TM and Clark, BC. Blood flow restricted exercise and skeletal muscle health. *Exerc Sport Sci Rev* 37: 78–85, 2009.
63. Manini, TM, Vincent, KR, Leeuwenburgh, CL, Lees, HA, Kavazis, AN, Borst, SE, and Clark, BC. Myogenic and proteolytic mRNA expression following blood flow restricted exercise. *Acta Physiol (Oxf)* 201: 255–263, 2011.
64. Mazzeo, R. Catecholamine responses to acute and chronic exercise. *Med Sci Sports Exerc* 23: 839–845, 1991.
65. McCall, GE, Byrnes, WC, Fleck, SJ, Dickinso, A, and Kraemer, WJ. Acute and chronic hormonal responses to resistance training designed to promote muscle hypertrophy. *Can J Appl Physiol* 24: 96–107, 1999.
66. Michel, RN, Dunn, SE, and Chin, ER. Calcineurin and skeletal muscle growth. *Proc Nutr Soc* 63: 341–349, 2004.

67. Moore, D, Burgomaster, K, Schofield, L, Gibala, M, Sale, D, and Phillips, S. Neuromuscular adaptations in humans muscle following low intensity resistance training with vascular occlusion. *Eur J Appl Physiol* 92: 399–406, 2004.
68. Moritani, T, Michael-Sherman, W, Shibata, M, Matsumoto, T, and Shinohara, M. Oxygen availability and motor unit activity in humans. *Eur J Appl Physiol Occup Physiol* 64: 552–556, 1992.
69. Nakajima, T, Kurano, M, Iida, H, Takano, H, Oonuma, H, Morita, T, Meguro, K, Sato, Y, and Nagata, T, and KAATSU Training Group. Use and safety of Kaatsu training: Results of a national survey. *Int J KAATSU Training Res* 2: 5–13, 2006.
70. Nielsen, JL, Aagaard, P, Bech, RD, Nygaard, T, Hyid, LG, Wernborn, M, Suetta, C, and Frandsen, U. Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. *J Physiol* 590: 4351–4361, 2012.
71. Nosaka, K, Newton, M, and Sacco, P. Delayed-onset muscle soreness does not reflect the magnitude of eccentric-exercise-induced muscle damage. *Scand J Med Sci Sports* 12: 337–346, 2002.
72. Park, S, Kim, JK, Choi, HM, Kim, HG, Beekley, MD, and Nho, H. Increase in maximal oxygen uptake following 2-week walk training with blood flow occlusion in athletes. *Eur J Appl Physiol* 109: 591–600, 2010.
73. Patterson, SD and Ferguson, RA. Increase in calf post-occlusive blood flow and strength following short-term resistance exercise training with blood flow restriction in young women. *Eur J Appl Physiol* 108: 1025–1033, 2010.
74. Pierce, J, Clark, B, Ploutz-Snyder, L, and Kanaley, J. Growth hormone and muscle function response to skeletal muscle ischemia. *J Appl Physiol* 101: 1588–1595, 2006.
75. Piwien-Pilipuk, G, Huo, JS, and Schwartz, J. Growth hormone signal transduction. *J Pediatr Endocrinol Metab* 15: 771–786, 2002.
76. Reeves, G, Kraemer, R, Hollander, D, Clavier, J, Thomas, C, Francois, M, and Castracane, VD. Comparison of hormone responses following light resistance exercise with partial vascular occlusion and moderately difficult resistance exercise without occlusion. *J Appl Physiol* 101: 1616–1622, 2006.
77. Renzi, CP, Tanaka, H, and Sugawara, J. Effects of leg blood flow restriction during walking on cardiovascular function. *Med Sci Sports Exerc* 42: 726–732, 2010.
78. Robergs, R, Ghiasvand, F, and Parker, D. Biochemistry of exercise-induced metabolic acidosis. *Am J Physiol Regul Integr Comp Physiol* 287: 502–516, 2004.
79. Rossow, LM, Fahs, CA, Sherk, VD, Seo, D, Bembem, DA, and Bembem, MG. The effect of acute blood-flow-restricted resistance exercise on post-exercise blood pressure. *Clin Physiol Funct Imaging* 31: 429–434, 2011.
80. Sale, DG. Influence of exercise and training on motor unit activation. *Exerc Sport Sci Rev* 15: 95–151, 1987.
81. Schott, J, McCully, K, and Rutherford, OM. The role of metabolites in strength training II. Short versus long isometric contractions. *Eur J Appl Physiol Occup Physiol* 71: 337–341, 1995.
82. Semenza, G. HIF-1: Mediator of physiological and pathophysiological responses to hypoxia. *J Appl Physiol* 88: 1474–1480, 2000.
83. Shinohara, M, Kouzaki, M, Yoshihisa, T, and Fukunaga, T. Efficacy of tourniquet ischemia for strength training with low resistance. *Eur J Appl Physiol Occup Physiol* 77: 189–191, 1998.
84. Suga, T, Okita, K, Morita, N, Yokota, T, Hirabayashi, K, Horiuchi, M, Takada, S, Takahashi, T, Omokawa, M, Kinugawa, S, and Tsutsui, H. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* 106: 1119–1124, 2009.
85. Suga, T, Okita, K, Takarada, S, Omokawa, M, Kadoguchi, T, Yokota, T, Hirabayashi, K, Takahashi, M, Morita, N, Horiuchi, M, and Kinugawa, S. Effect of multiple sets on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *Eur J Appl Physiol* 112: 3915–3920, 2012.
86. Sumide, T, Sakuraba, K, Sawaki, K, Ohmura, H, and Tamura, Y. Effect of resistance exercise training combined with relatively low vascular occlusion. *J Sci Med Sport* 12: 107–112, 2009.
87. Suzuki, YJ and Ford, GD. Redox regulation of signal transduction in cardiac and smooth muscle. *J Mol Cell Cardiol* 31: 345–353, 1999.
88. Takano, H, Morita, T, Iida, H, Asada, K, Kato, M, Uno, K, Hirose, K, Matsumoto, A, Takenaka, K, Hirata, Y, Eto, F, Nagai, R, Sato, Y, and Nakajima, T. Hemodynamic and hormonal response to a short-term low-intensity resistance exercise with a reduction in muscle blood flow. *Eur J Appl Physiol* 95: 65–73, 2005.
89. Takarada, Y, Nakamura, Y, Aruga, S, Onda, T, Miyazaki, S, and Ishii, N. Rapid increase in plasma growth hormone after low-intensity exercise with vascular occlusion. *J Appl Physiol* 88: 61–65, 2000.
90. Takarada, Y, Sato, Y, and Ishii, N. Effects of resistance exercise combined with vascular occlusion on muscle function in athletes. *Eur J Appl Physiol* 86: 308–314, 2002.
91. Takarada, Y, Takazawa, H, Sato, Y, Takebayashi, S, Tanaka, Y, and Ishii, N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J Appl Physiol* 88: 2097–2106, 2000.
92. Tanimoto, M, Madarame, H, and Ishii, N. Muscle oxygenation and plasma growth hormone concentration during and after resistance exercise: Comparison between "KAATSU" and other types of regimen. *Int J KAATSU Training Res* 1: 51–56, 2005.
93. Tsutsumi, YM, Yokoyama, T, Horikawa, Y, Roth, DM, and Patel, HH. Reactive oxygen species trigger ischemic and pharmacological postconditioning: In vivo and in vitro characterization. *Life Sci* 81: 1223–1227, 2007.
94. Uchiyama, S, Tsukamoto, H, Yoshimura, S, and Tamaki, T. Relationship between oxidative stress in muscle tissue and weightlifting-induced muscle damage. *Pflugers Arch* 452: 109–116, 2006.
95. Umbel, JD, Hoffman, RL, Dearth, DJ, Chelboun, GS, Manini, TM, and Clark, BC. Delayed-onset muscle soreness induced by low-load blood flow-restricted exercise. *Eur J Appl Physiol* 107: 687–695, 2009.
96. Wernbom, M, Augustsson, J, and Thomee, R. Effects of vascular occlusion on muscular endurance in dynamic knee extension exercise at different submaximal loads. *J Strength Cond Res* 20: 372–377, 2006.
97. Wernbom, M, Jarrebring, R, Andreasson, MA, and Augustsson, J. Acute effects of blood flow restriction on muscle fatiguing dynamic knee extensions at low load. *J Strength Cond Res* 23: 2389–2395, 2009.
98. Wernbom, M, Paulsen, NG, Nilsen, T, Hisdal, J, and Raastad, T. Contractile function and sarcolemmal permeability after acute low-load resistance exercise with blood flow restriction. *Eur J Appl Physiol* 112: 2051–2063, 2012.
99. Victor, RG and Seales, DR. Reflex stimulation of sympathetic outflow during rhythmic exercise in human. *Am J Physiol* 257: 2017–2024, 1989.
100. Yasuda, T, Brechue, WF, Fujita, T, Shirakawa, J, Sato, Y, and Abe, T. Muscle activation during low-intensity muscle contractions with restricted blood flow. *J Sports Sci* 27: 479–489, 2009.
101. Yasuda, T, Fujita, T, Miyagi, Y, Kubota, Y, Sato, Y, Nakajima, M, Bembem, M, and Abe, T. Electromyographic response of arm and chest muscle during bench press exercise with and without KAATSU. *Int J KAATSU Training Res* 2: 15–18, 2006.
102. Yasuda, T, Ogasawara, R, Sakamaki, M, Bembem, MG, and Abe, T. Relationship between limb and trunk muscle hypertrophy following high intensity resistance training and blood flow restricted low intensity resistance training. *Clin Physiol Funct Imaging* 31: 347–351, 2011.