

Blood flow restriction pressure recommendations: The hormesis hypothesis



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ABSTRACT

Blood flow restriction (BFR) alone or in combination with exercise has been shown to result in favorable effects on skeletal muscle form and function. The pressure applied should be high enough to occlude venous return from the muscle but low enough to maintain arterial inflow into the muscle. The optimal pressure for beneficial effects on skeletal muscle are currently unknown; however, preliminary data from our laboratory suggests that there may be a point where greater pressure may not augment the response (e.g. metabolic accumulation, cell swelling) but may actually result in decrements (e.g. muscle activation). This led us to wonder if BFR elicits somewhat of a hormesis effect. The purpose of this manuscript is to discuss whether pressure may be modulated to maximize skeletal muscle adaptation with resistance training in combination with BFR. Furthermore, the potential safety issues that could arise from increasing pressure too high are also briefly reviewed. We hypothesize that with BFR there is likely a moderate (~50% estimated arterial occlusion pressure) pressure that maximizes the anabolic response to skeletal muscle without producing the potential negative consequences of higher pressures. Thus, BFR may follow the hormesis theory to some degree, in that a low/moderate dose of BFR produces beneficial effects while higher pressures (at or near arterial occlusion) may decrease the benefits of exercise and increase the health risk. This hypothesis requires long term studies investigating chronic training adaptations to differential pressures. In addition, how differences in load interact with differences in pressure should also be investigated.

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Introduction

Blood flow restriction (BFR) alone or in combination with low-intensity exercise results in favorable effects on skeletal muscle form and function [1] and preliminary evidence suggests it may also promote bone formation [2,3]. These positive effects on skeletal muscle have been observed across a wide variety of populations (e.g. athletes, untrained, elderly, patients in rehabilitation), and thus, BFR in combination with low-intensity exercise represents a powerful tool in promoting an increase in skeletal muscle growth and strength. The mechanisms behind these effects are thought to be dependent upon how the stimulus is applied (i.e. BFR alone vs. BFR + Aerobic Exercise vs. BFR + Resistance Exercise); however, a foundational mechanism may be the acute increase in muscle cell swelling following the application of BFR alone [4] or in combination with aerobic [5] or resistance exercise [6]. Further proposed mechanisms behind the effects of low load resistance exercise in

combination with BFR include increased fiber type recruitment from metabolic accumulation [7], decreased myostatin [8], decreased atrogenes [9], and the proliferation of satellite cells [10].

BFR is a stimulus commonly applied with specialized pressure cuffs placed at the top of a limb which are inflated to a set pressure throughout exercise. Theoretically, the pressure applied should be high enough to occlude venous return from the muscle but low enough to maintain arterial inflow into the muscle. It is clear that the pressure should not be universally applied as has been done previously, but should be individualized to the person in some way [11]. The optimal pressure for beneficial effects on skeletal muscle is currently unknown. Interestingly, preliminary data from our laboratory suggests that there may be a point where greater pressure may not augment the response but may actually result in decrements (e.g. muscle activity). This led us to wonder if BFR elicits somewhat of a hormesis effect. Hormesis is traditionally defined as a theoretical phenomenon of dose-response relationships in which something that produces harmful biological effects at moderate to high doses may produce beneficial effects at low doses [12]. With respect to BFR, it may be that low and high levels of cuff pressure may be ineffective in augmenting the skeletal muscle

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response. However, with high levels of BFR cuff pressure, there may be safety consequences beyond the absence of an augmented skeletal muscle response. In other words, low to moderate pressures may be safe but it may be that only moderate pressures are able to elicit favorable skeletal muscle responses. Although this may not be hormesis as it is traditionally defined, we hypothesize that there is likely a pressure that is optimal for both safety and effectiveness. The purpose of this manuscript is to discuss whether pressure may be modulated to maximize acute changes in predictors of chronic skeletal muscle adaptation with resistance training in combination with BFR. Furthermore, the potential safety issues that could arise from increasing pressure too high are also briefly reviewed.

Cell swelling

A number of studies have observed acute increases in markers of muscle swelling following the application of BFR with and without exercise [4–6,13–16]. This muscle cell swelling has been hypothesized previously to be the foundational mechanism behind the application of BFR because it is observed even in the absence of exercise [4,17]. The acute increase in muscle thickness coupled with the decrease in plasma volume suggests that fluid may shift from the plasma to inside the muscle cell [4]. For example, if the acute change in muscle thickness was due solely to venous pooling, the muscle thickness value would have returned to baseline in the BFR conditions following the removal of the cuff. The theory behind the cell swelling induced changes in protein balance was introduced by Haussinger et al. [18]. Based on Haussinger's hypothetical model for hepatocyte cell swelling [19], it has been theorized that BFR induced muscle cell swelling is detected by an intrinsic volume sensor. The activation of this volume sensor may lead to an activation of the mammalian target of rapamycin (mTOR) and mitogen-activated protein-kinase (MAPK) pathways [20]. These pathways are activated with BFR and exercise; however, it is unknown whether these pathways are activated with BFR in the absence of exercise. Preliminary research from our laboratory suggests that skeletal muscle can only acutely increase a finite amount suggesting that muscle cell swelling may be a requisite for muscle growth but in and of itself is not sufficient. Data from Takarada et al. [21] seems to support this finding given that the application of BFR in the absence of exercise attenuates atrophy but does not completely maintain or promote muscle growth. What is currently unknown is what pressure maximizes this muscle cell swelling response. We hypothesize that the cell swelling response with BFR likely occurs with low pressures; with higher pressures not further increasing acute muscle cell size. It should be noted that these proposed mechanisms for BFR induced muscle cell swelling are currently only conjecture and future cellular studies are needed to confirm that (1) the fluid shift resulted in an actual increase in muscle cell size and not just an increase in interstitial fluid and (2) if true, to determine the mechanisms behind the increase in acute muscle cell size.

Whole blood lactate

A number of studies have observed increases in whole blood lactate following low load resistance exercise in combination with BFR [7,15,22–27]. The increase in whole blood lactate occurs due to fast glycolysis and the accumulation of this lactate along with other metabolites has been hypothesized to play an important role in skeletal muscle adaptation through increased muscle fiber recruitment [28,29]. This increase in lactate may also facilitate the increase in growth hormone observed following resistance exercise with BFR [27], although the skeletal muscle anabolic effect

of growth hormone in adults is largely unfounded [30,31]. Of those studies investigating the acute increases in lactate following BFR in combination with resistance exercise, only one has investigated those changes across different pressures (100 mmHg vs. 160 mmHg) and it was completed in the upper body. To illustrate, Yasuda et al. [7] investigated unilateral elbow flexion muscle contractions completed at 20% 1RM (30 repetitions, followed by 3 sets of 15) and 70% 1RM (3 sets to failure). The 160 mmHg condition had a greater increase in lactate than the 100 mmHg condition, but the non-BFR 70% 1RM condition had the greatest increase in lactate. The authors suggested that this difference is unlikely due to differences in tissue oxygenation levels since venous oxygen partial pressure and venous oxygen saturation were similar between all exercise conditions. Instead, it seems more likely that 70% 1RM requires a greater dependence on oxygen-independent metabolism than muscle contractions performed at 20% 1RM, indicating a greater energetic demand with higher loads. We hypothesize that the metabolic stress with BFR likely increases with increasing pressure, but there is likely a point where the response is no longer augmented. This should be further investigated to determine the dose response to applied pressure. In addition, it may be important to consider that metabolic accumulation determined by whole blood lactate may not necessarily reflect the amount accumulating distal to the cuff. Furthermore, this metabolic stress response may also be affected by load as one group has found that BFR in combination with 30%1RM [32] but not 20% 1RM [33] produces responses similar to that observed with higher load exercise.

Electromyography

A number of studies have observed increases in EMG amplitude during low load resistance exercise with BFR [6,9,15,16,23,34–38]. The increase in EMG amplitude may be due to this metabolic “overload” (i.e. depletion of phosphocreatine stores and decrease in muscle pH) within the muscle [32]. To illustrate, the reduction in oxygen and subsequent metabolic accumulation with muscle contraction and/or BFR may increase fiber recruitment through a stimulation of the group III and IV afferents which may cause an inhibition of the alpha motor neuron, resulting in an increased fiber recruitment to maintain force and protect against conduction failure [7]. Of those studies investigating the acute increases in EMG amplitude following BFR in combination with resistance exercise, only one has investigated those changes across different pressures (80%, 100%, and 120% of bSBP) and it was completed in the upper body [16]. Following cuff inflation, participants performed four sets of dumbbell elbow flexion exercise with 30 seconds rest between each set. The first set consisted of 30 repetitions followed by 3 sets of 15 at 20% 1RM. They found that integrated EMG increased progressively during the contraction bout in all groups. However, they found that amplitude was greater with 120% bSBP than a work matched non-BFR condition from the end of 30 repetitive contracts to the end of the second set of 15 contractions. Recent preliminary data from our group demonstrates that increasing pressure may augment muscle activation to a point, and then it results in no further increase and a trend towards lower activation. More research is needed, but this preliminary data suggests that low to moderate pressure may stimulate muscle activation whereas pressure closer to arterial occlusion may begin to inhibit it to some degree.

Acute fatigue

A number of studies have observed large acute drops in torque following low load resistance exercise in combination with BFR

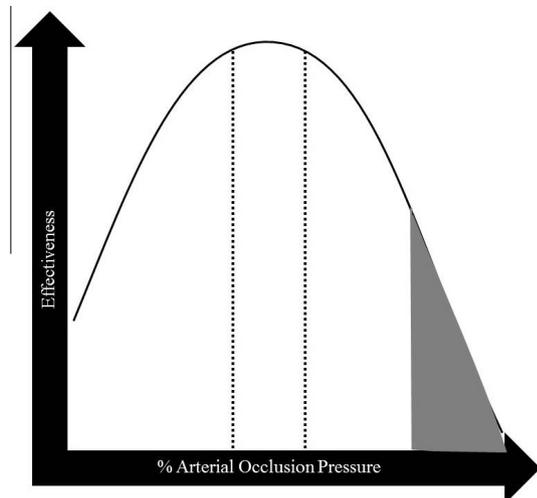


Fig. 1. A theoretical diagram demonstrating the proposed optimal pressure that maximizes both effectiveness and safety of blood flow restricted exercise. The gray portion of the figure indicates the range where the pressure increases to the point of potential health concern.

[14,23,34,37,39–42]. This large acute drop immediately post exercise appears to be evidence of fatigue, not muscle damage. This increased fatigability is thought to provide at least part of the mechanistic rationale for BFR inducing skeletal muscle hypertrophy when it is combined with resistance exercise [43]. The mechanisms may include an increase in intramuscular inorganic phosphate concentration, as this has been previously observed to occur following four sets of resistance exercise in combination with BFR [44]. This accumulation of inorganic phosphate may lead to a decline in the amplitude of the calcium transient and an inhibition of the cross-bridge cycle [45]. Of those studies investigating the acute drop in torque following BFR in combination with lower body resistance exercise, only one [40] has investigated those changes across different pressures (130% systolic blood pressure (SBP) vs. 300 mmHg) as well as loads (20% MVC vs. 40% MVC). In that study, participants completed three sets of knee extension exercise to failure with each load (20% MVC vs. 40% MVC) and pressure (130% SBP vs. 300 mmHg). The results indicated that 20% MVC with a pressure 130% SBP (~160 mmHg) resulted in a greater percentage decrease in MVC compared with the high load (80% MVC) condition without BFR. There were no other significant differences between conditions. Due to reporting only percent changes in MVC from baseline, the acute torque data from that study should be interpreted with caution, since percent change is unable to determine the actual magnitude of the effect [46]. We hypothesize that the acute fatigue with BFR likely increases with increasing pressure; although, there is likely a point where the response is no longer augmented. In fact the aforementioned study found that the acute fatigue response was not augmented when pressure was increased to 300 mmHg [40]. This should be further investigated to determine the dose response to applied pressure.

Possible safety issues

The potential concern with increasing pressure too high is that arterial blood flow maybe completely removed during the rest periods between sets and possibly during the exercise itself. Complete arterial occlusion during the rest periods of resistance exercise has been observed when using wide cuffs set at 130% of bSBP [47]. This greater reduction in blood flow with a wider cuff was also accompanied by a greater cardiovascular demand compared to a narrow cuff inflated to the same pressure (wider

cuff, more restriction). Complete arterial occlusion is a safety concern because this can cause the formation of a thrombus and can induce a microvascular occlusion even after reperfusion [48]. This post-reperfusion occlusion could result in muscle damage and/or cell necrosis [49,50]. Further, the risk for thrombus formation may be increased if the exercise is completed to muscular failure [51], which is not uncommon in the literature [36,41,42,52]. In addition to thrombus formation, inappropriate levels of compression may cause a slowing of nerve conduction velocity which would be detrimental for long duration training [53,54]. Furthermore, complete arterial occlusion may decrease the effectiveness of the training intervention by decreasing the volume of work that the individual is able to complete [40]. Since volume appears to be the important factor behind chronic changes in skeletal muscle size [55], any factor decreasing this variable would be disadvantageous for skeletal muscle.

Conclusions

There are numerous beneficial skeletal muscle effects from the application of BFR with low load exercise. We wish to suggest that there is data that demonstrates that increasing pressure results in an augmentation in the acute response to predictors of muscle growth, independent of the load lifted. We hypothesize that with BFR there is likely a moderate (~50% estimated arterial occlusion pressure) pressure that maximizes the anabolic response to skeletal muscle without producing the potential negative consequences of higher pressures (Fig. 1). Thus, BFR may follow the hormesis theory to some degree, in that a low/moderate dose of BFR produces beneficial effects while higher pressures (at or near arterial occlusion) may decrease the benefits of exercise and increase the health risk. This hypothesis requires long term studies investigating chronic training adaptations to differential pressures. In addition, how differences in load interact with differences in pressure should also be investigated.

Conflict of interest

The authors report no conflict of interest.

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References

- [1] Loenneke JP, Abe T, Wilson JM, et al. Blood flow restriction: an evidence based progressive model (review). *Acta Physiol Hung* 2012;99:235–50.
- [2] Loenneke JP, Young KC, Wilson JM, Andersen JC. Rehabilitation of an osteochondral fracture using blood flow restricted exercise: a case review. *J Bodyw Mov Ther* 2013;17:42–5.
- [3] Beekley MD, Sato Y, Abe T. KAATSU-walk training increases serum bone-specific alkaline phosphatase in young men. *Int J KAATSU Training Res* 2005;1:77–81.
- [4] Loenneke JP, Fahs CA, Thiebaud RS, et al. The acute muscle swelling effects of blood flow restriction. *Acta Physiol Hung* 2012;99:400–10.
- [5] Ogawa M, Loenneke JP, Yasuda T, et al. Time course changes in muscle size and fatigue during walking with restricted leg blood flow in young men. *JPEM* 2012;3:14–9.
- [6] Yasuda T, Loenneke JP, Thiebaud RS, Abe T. Effects of blood flow restricted low-intensity concentric or eccentric training on muscle size and strength. *PLoS One* 2012;7:e52843.
- [7] Yasuda T, Abe T, Brechue WF, et al. Venous blood gas and metabolite response to low-intensity muscle contractions with external limb compression. *Metabolism* 2010;59:1510–9.

- [8] Laurentino GC, Ugrinowitsch C, Roschel H, et al. Strength training with blood flow restriction diminishes myostatin gene expression. *Med Sci Sports Exerc* 2012;44:406–12.
- [9] Manini TM, Vincent KR, Leeuwenburgh CL, et al. Myogenic and proteolytic mRNA expression following blood flow restricted exercise. *Acta Physiol (Oxf)* 2011;201:255–63.
- [10] Nielsen JL, Aagaard P, Bech RD, et al. Proliferation of myogenic stem cells in human skeletal muscle in response to low-load resistance training with blood flow restriction. *J Physiol* 2012;590:4351–61.
- [11] Loenneke JP, Fahs CA, Rossow LM, et al. Blood flow restriction pressure recommendations: a tale of two cuffs. *Front Physiol* 2013;4:249.
- [12] Radak Z, Chung HY, Koltai E, Taylor AW, Goto S. Exercise, oxidative stress and hormesis. *Ageing Res Rev* 2008;7:34–42.
- [13] Fry CS, Glynn EL, Drummond MJ, et al. Blood flow restriction exercise stimulates mTORC1 signaling and muscle protein synthesis in older men. *J Appl Physiol* 2010;108:1199–209.
- [14] Thiebaud RS, Yasuda T, Loenneke JP, Abe T. Effects of low-intensity concentric and eccentric exercise combined with blood flow restriction on indices of exercise-induced muscle damage. *Interv Med Appl Sci* 2013;5:53–9.
- [15] Wilson JM, Lowery RP, Joy JM, Loenneke JP, Naimo MA. Practical blood flow restriction training increases acute determinants of hypertrophy without increasing indices of muscle damage. *J Strength Cond Res* 2013;27:3068–75.
- [16] Yasuda T, Brechue WF, Fujita T, Sato Y, Abe T. Muscle activation during low-intensity muscle contractions with varying levels of external limb compression. *J Sports Sci Med* 2008;7:467–74.
- [17] Loenneke JP, Abe T, Wilson JM, Ugrinowitsch C, Bembem MG. Blood flow restriction: how does it work? *Front Physiol* 2012;3:392.
- [18] Haussinger D, Roth E, Lang F, Gerok W. Cellular hydration state: an important determinant of protein catabolism in health and disease. *Lancet* 1993;341:1330–2.
- [19] Haussinger D. The role of cellular hydration in the regulation of cell function. *Biochem J* 1996;313(Pt 3):697–710.
- [20] Loenneke JP, Fahs CA, Rossow LM, Abe T, Bembem MG. The anabolic benefits of venous blood flow restriction training may be induced by muscle cell swelling. *Med Hypotheses* 2012;78:151–4.
- [21] Takarada Y, Takazawa H, Ishii N. Applications of vascular occlusion diminish disuse atrophy of knee extensor muscles. *Med Sci Sports Exerc* 2000;32:2035–9.
- [22] Fujita S, Abe T, Drummond MJ, et al. Blood flow restriction during low-intensity resistance exercise increases S6K1 phosphorylation and muscle protein synthesis. *J Appl Physiol* 2007;103:903–10.
- [23] Labarbera KE, Murphy BG, Laroche DP, Cook SB. Sex differences in blood flow restricted isotonic knee extensions to fatigue. *J Sports Med Phys Fitness* 2013;53:444–52.
- [24] Loenneke JP, Balapur A, Thrower AD, Barnes JT, Pujol TJ. Blood flow restriction reduces time to muscular failure. *Eur J Sport Sci* 2012;12:238–43.
- [25] Loenneke JP, Wilson JM, Balapur A, Thrower AD, Barnes JT, Pujol TJ. Time under tension decreased with blood flow-restricted exercise. *Clin Physiol Funct Imaging* 2012;32:268–73.
- [26] Takano H, Morita T, Iida H, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur J Appl Physiol* 2005;95:65–73.
- [27] Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, Ishii N. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 2000;88:61–5.
- [28] Loenneke JP, Fahs CA, Wilson JM, Bembem MG. Blood flow restriction: the metabolite/volume threshold theory. *Med Hypotheses* 2011;77:748–52.
- [29] Schoenfeld BJ. Potential mechanisms for a role of metabolic stress in hypertrophic adaptations to resistance training. *Sports Med* 2013;43:179–94.
- [30] Rennie MJ, Wackerhage H, Spangenburg EE, Booth FW. Control of the size of the human muscle mass. *Annu Rev Physiol* 2004;66:799–828.
- [31] Birzniece V, Nelson AE, Ho KK. Growth hormone administration: is it safe and effective for athletic performance. *Endocrinol Metab Clin North Am* 2010;39:11–23 [viii].
- [32] Suga T, Okita K, Morita N, et al. Dose effect on intramuscular metabolic stress during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* 2010;108:1563–7.
- [33] Suga T, Okita K, Morita N, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* 2009;106:1119–24.
- [34] Cook SB, Murphy BG, Labarbera KE. Neuromuscular function following a bout of Low-load blood flow restricted exercise. *Med Sci Sports Exerc* 2013;45:67–74.
- [35] Takarada Y, Takazawa H, Sato Y, Takebayashi S, Tanaka Y, Ishii N. Effects of resistance exercise combined with moderate vascular occlusion on muscular function in humans. *J Appl Physiol* 2000;88:2097–106.
- [36] Wernbom M, Jarrebring R, Andreasson MA, Augustsson J. Acute effects of blood flow restriction on muscle activity and endurance during fatiguing dynamic knee extensions at low load. *J Strength Cond Res* 2009;23:2389–95.
- [37] Yasuda T, Brechue WF, Fujita T, Shirakawa J, Sato Y, Abe T. Muscle activation during low-intensity muscle contractions with restricted blood flow. *J Sports Sci* 2009;27:479–89.
- [38] Yamada E, Kusaka T, Tanaka S, Mori S, Norimatsu H, Itoh S. Effects of vascular occlusion on surface electromyography and muscle oxygenation during isometric contraction. *J Sport Rehabil* 2004;13:287–99.
- [39] Loenneke JP, Thiebaud RS, Fahs CA, Rossow LM, Abe T, Bembem MG. Blood flow restriction does not result in prolonged decrements in torque. *Eur J Appl Physiol* 2013;113:923–31.
- [40] Cook SB, Clark BC, Ploutz-Snyder LL. Effects of exercise load and blood-flow restriction on skeletal muscle function. *Med Sci Sports Exerc* 2007;39:1708–13.
- [41] Wernbom M, Paulsen G, Nilsen TS, Hisdal J, Raastad T. Contractile function and sarcolemmal permeability after acute low-load resistance exercise with blood flow restriction. *Eur J Appl Physiol* 2012;112:2051–63.
- [42] Umbel JD, Hoffman RL, Dearth DJ, Chleboun GS, Manini TM, Clark BC. Delayed-onset muscle soreness induced by low-load blood flow-restricted exercise. *Eur J Appl Physiol* 2009;107:687–95.
- [43] Loenneke JP, Wilson GJ, Wilson JM. A mechanistic approach to blood flow occlusion. *Int J Sports Med* 2010;31:1–4.
- [44] Sugaya M, Yasuda T, Suga T, Okita K, Abe T. Change in intramuscular inorganic phosphate during multiple sets of blood flow-restricted low-intensity exercise. *Clin Physiol Funct Imaging* 2011;31:411–3.
- [45] Fitts RH. The cross-bridge cycle and skeletal muscle fatigue. *J Appl Physiol* 2004;104:551–8.
- [46] Rhea MR. Determining the magnitude of treatment effects in strength training research through the use of the effect size. *J Strength Cond Res* 2004;18:918–20.
- [47] Rossow LM, Fahs CA, Loenneke JP, et al. Cardiovascular and perceptual responses to blood-flow-restricted resistance exercise with differing restrictive cuffs. *Clin Physiol Funct Imaging* 2012;32:331–7.
- [48] Loenneke JP, Wilson JM, Wilson GJ, Pujol TJ, Bembem MG. Potential safety issues with blood flow restriction training. *Scand J Med Sci Sports* 2011;21:510–8.
- [49] Harman JW. The significance of local vascular phenomena in the production of ischemic necrosis in skeletal muscle. *Am J Pathol* 1948;24:625–41.
- [50] Strock PE, Majno G. Microvascular changes in acutely ischemic rat muscle. *Surg Gynecol Obstet* 1969;129:1213–24.
- [51] Wallen NH, Goodall AH, Li N, Hjelm Dahl P. Activation of haemostasis by exercise, mental stress and adrenaline: effects on platelet sensitivity to thrombin and thrombin generation. *Clin Sci (Lond)* 1999;97:27–35.
- [52] Takarada Y, Sato Y, Ishii N. Effects of resistance exercise combined with vascular occlusion on muscle function in athletes. *Eur J Appl Physiol* 2002;86:308–14.
- [53] Mittal P, Shenoy S, Sandhu JS. Effect of different cuff widths on the motor nerve conduction of the median nerve: an experimental study. *J Orthop Surg Res* 2008;3:1.
- [54] Pedowitz RA, Nordborg C, Rosenqvist AL, Rydevik BL. Nerve function and structure beneath and distal to a pneumatic tourniquet applied to rabbit hindlimbs. *Scand J Plast Reconstr Surg Hand Surg* 1991;25:109–20.
- [55] Mitchell CJ, Churchward-Venne TA, West DW, et al. Resistance exercise load does not determine training-mediated hypertrophic gains in young men. *J Appl Physiol* 2012;113:71–7.