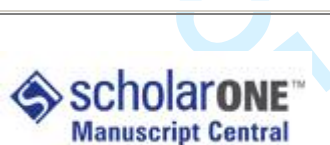




Ischemic Strength Training: A Low-Load Alternative to Heavy Resistance Exercise?

Journal:	<i>Scandinavian Journal of Medicine and Science in Sports</i>
Manuscript ID:	draft
Manuscript Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Wernbom, Mathias; Lundberg laboratory for human muscle function and movement analysis, Department of orthopaedics
Keywords:	Strength training, Ischemia , Vascular occlusion, Muscle hypertrophy, Muscle atrophy



Ischemic Strength Training: A Low-Load Alternative to Heavy Resistance Exercise?

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Key words: strength training, ischemia, vascular occlusion, muscle hypertrophy, muscle atrophy

Abstract

Strength training with low loads in combination with vascular occlusion has been proposed as an alternative to heavy resistance exercise in the rehabilitation setting, especially when high forces acting upon the musculoskeletal system are contraindicated. Several studies on low to moderate-intensity resistance exercise combined with cuff occlusion have demonstrated increases in muscle strength and size that are comparable to those typically seen after conventional high-load strength training. However, the physiological mechanisms by which occlusion training induces increased muscle mass and strength are currently unclear, although several candidate stimuli have been proposed. Also, the long-term safety, practicality and efficacy of this training method are still controversial. Furthermore, recent studies have demonstrated that in some instances, tourniquet cuffs may not be necessary for relative ischemia and significant training effects to occur with resistance exercise at low to moderate loads. The aims of the present review are to summarize current opinion and knowledge regarding the physiology of ischemic strength training and to discuss some of the training and health aspects of this type of exercise. In addition, suggestions for further research are given.

Introduction

Strength training is an important component of training in most sports as well as in the area of injury prevention and rehabilitation (Escamilla & Wickham, 2003). In the prescription of resistance exercise, training intensity or the load used is commonly regarded as the most important variable (Fleck & Kraemer, 1997). The intensity in dynamic resistance training is often quantified as a function of the maximum weight that can be lifted only once (one repetition maximum, 1RM). Most authors agree that the load should be at least 60% of 1RM in order to stimulate increases in strength and that optimal strength gains results from loads in excess of 80% of 1RM (Atha, 1981; Häkkinen, 1994; Fleck & Kraemer, 1997; ACSM, 2002; Andersen et al, 2006). For muscle hypertrophy, loads of 6-12RM are usually recommended, corresponding to ~70-85% of 1RM (Häkkinen, 1994; Fleck & Kraemer, 1997; ACSM, 2002).

In the clinical setting, however, it is often difficult and sometimes also contraindicated to use near-maximal loads (e.g. early rehabilitation after a sports injury). Muscle atrophy and weakness often occur rapidly in the affected area due to the effects of trauma (or disease) and inactivity. Consequently, training modalities that promote hypertrophy or counteract atrophy without the use of heavy loads should be of special interest in the rehabilitation of injuries and some chronic diseases for which high musculoskeletal forces are contraindicated.

In the mid 1990's, Rooney et al. (1994) and Schott et al. (1995) suggested that fatigue and metabolite accumulation were important factors in the resistance exercise stimulus leading to increased strength and accretion of muscle mass. These findings were extended by Shinohara et al. (1998) and Takarada et al. (2000b), who used tourniquet cuffs to partially restrict the muscle blood flow during training with low resistance in order to cause increases in muscle strength. In these and in several subsequent studies (Takarada et al., 2002, 2004; Burgomaster et al., 2003; Abe et al, 2005a, b; Kubo et al., 2006) low to moderate intensity (20-50% of 1RM) resistance training with vascular occlusion has been shown to lead to gains

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3 in muscle strength and volume comparable to those seen after conventional heavy resistance
4 training. In one recent study, hypertrophy of the quadriceps was even observed after walk
5 training with tourniquets (Abe et al., 2006). It has also been reported that brief intermittent
6 tourniquet-induced ischemia-reperfusion, without exercise, can decrease disuse atrophy; at
7 least in some muscles (Takarada et al., 2000c; Clark et al., 2006, Kubota et al., 2008).
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15 The combination of low loads and large training effects suggests that ischemic strength
16 training may be a useful method in rehabilitation and other contexts. However, the practicality
17 and the safety of training with vascular occlusion remain controversial. Therefore, the purpose
18 of the present review is to summarize current opinion and knowledge regarding the
19 physiology of ischemic strength training and to discuss some of the training and health
20 aspects of this type of exercise.
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33 **Physiology**

34 **Motor unit recruitment**

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37 It is generally believed that only muscle fibers that are activated during exercise grow as a
38 result of strength training (Kraemer, Fleck & Evans, 1996). The size principle of motor unit
39 recruitment dictates that small units composed of slow but fatigue resistant fibers are recruited
40 first and with increasing demands for force or power, ever larger units are recruited
41 (Henneman et al., 1965). Studies using glycogen depletion (Gollnick et al., 1974a, b;
42 Vøllestad et al., 1984, 1985) and alterations in phosphocreatine-to-creatine ratios in muscle
43 fibers (Beltman et al., 2004a, b) have supported the notion that the size principle is operating
44 in humans during exercise. Thus, units with type I fibers are usually recruited first and with
45 increasing intensity of exercise, units comprised of type IIa fibers and finally also units with
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3 type IIx fibers are recruited (Beltman et al., 2004a). In relatively large limb muscles such as
4 the deltoid and the biceps brachii, recruitment of new motor units with increasing loads occurs
5 up to at least 80% of maximum voluntary isometric action (MVIA), and possibly even higher
6 (Basmajian & De Luca, 1985). Thus, it would appear that the heavy loads typically used in
7 resistance training regimes are required to ensure that most motor units are recruited and thus
8 exposed to the stimulus of strength training.
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17 However, numerous studies (e.g. Vøllestad et al., 1984; Sahlin et al., 1997, Houtman et
18 al., 2002, 2003) have shown that the recruitment thresholds for the motor units decrease
19 during fatiguing exercise at submaximal loads so that type II fibers are increasingly recruited
20 as the point of torque failure draws closer. Restricting the muscle blood flow with a tourniquet
21 has been shown to decrease the endurance and increase the electrical activity (as measured by
22 electromyography, EMG) of the working muscle during low intensity exercise. For example,
23 Takarada et al. (2000b) showed that the EMG of the biceps brachii during low-intensity
24 resistance exercise (40% of 1RM) combined with partial occlusion of the muscle blood flow
25 was almost equal to that observed during conventional heavy resistance exercise (80% of
26 1RM). In an early study on low-intensity dynamic knee extensions performed to exhaustion
27 during cuff occlusion, Ingemann-Hansen et al. (1981) observed glycogen depletion in both
28 fiber types as well as low creatine phosphate levels in muscle biopsies taken immediately
29 post-exercise before the release of the occlusion. Yasuda et al. (2005) reported type II fiber
30 hypertrophy as well as increased whole muscle cross-sectional area (CSA) after a period of
31 low intensity strength training (20% of 1RM) combined with vascular occlusion. Collectively,
32 these findings strongly suggest that type II fibers are recruited also during very low intensity
33 ischemic training. Indeed, it has been argued that the enhanced hypertrophic response to
34 exercise with blood flow restriction may simply be due to the recruitment of large motor units
35 and the resulting mechanical load on the muscle fibers in these units (Meyer, 2006).
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Response of hormones and systemic growth factors

Heavy resistance exercise can result in acute changes in the plasma levels of several hormones and growth factors. While some studies have also demonstrated changes in the resting levels of some hormones after short term training, it has been argued that the acute hormonal response is of greater importance for hypertrophic adaptations than chronic changes (Kraemer & Ratamess, 2005). Hormones and systemic growth factors that have been shown to increase acutely in plasma as a result of a strength training bout include growth hormone (GH), testosterone, cortisol, insulin-like growth factor 1 (IGF-1), insulin and catecholamines (Kraemer & Ratamess, 2005). To date, most of the research has been focused on the anabolic hormones GH and testosterone, and the catabolic hormone cortisol.

With low load occlusion training, very large acute increases in plasma GH have been demonstrated in some studies (Takarada et al., 2000a, 2004), which led these authors to speculate that GH may play a part in the muscle hypertrophy seen after this type of training. However, the evidence for a role for GH in exercise-induced muscle hypertrophy is limited. McCall et al. (1999) reported significant correlations between the acute increases in GH and the increases in type I and type II fiber area in the biceps brachii in response to a period of strength training, but there was no relationship between increases in GH and increases in whole muscle area for the biceps brachii. Goto et al. (2005) reported significant correlations between acute exercise-induced elevations in GH and increases in quadriceps cross sectional area (CSA) after a training period. While the correlations reported in the studies of McCall et al. (1999) and Goto et al. (2005) appear to support a role for GH, they do not prove causality. It is possible that the increased levels of GH reflected a greater level of effort, which in itself would likely be sufficient to cause increased growth. Additionally, elevated levels of GH may be caused by and/or occur in parallel to local processes which may be more important for the

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3 hypertrophic response. Furthermore, studies examining exogenous GH in combination with
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5 resistance exercise have generally not shown any significant additive effects on muscle
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7 anabolism (reviewed by Rennie, 2003). However, it should also be noted that there are several
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9 variants of growth hormone as well as other peptides that are released from the pituitary gland
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11 in response to resistance training (Hymer et al., 2006). Thus, the physiological significance of
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13 the GH response to both conventional and ischemic strength training is currently unclear.
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17 Many of the effects of GH are mediated by IGF-1. Originally, IGF-1 was regarded as a
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19 systemic growth factor produced by the liver under the influence of GH. During the last
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21 decades, it has become evident that GH also stimulates local IGF-1 production in the
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23 peripheral tissues, including muscle, and that GH itself has direct effects on local tissues
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25 (Goldspink et al., 2006). The acute response of circulating IGF-1 to resistance exercise is
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27 unclear (Kraemer & Ratamess 2005). In a recent study by Popov et al. (2006), a moderate
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29 intensity (50% of 1RM) leg press regime with no relaxation between repetitions and short
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31 inter-set rest periods (30 seconds) induced an acute increase in circulating IGF-1 levels, which
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33 was highly correlated with the increase in plasma GH. As will be discussed in a later section,
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35 this type of regime has many similarities with training combined with cuff occlusion.
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41 However, it seems unlikely that an acute increase in GH could cause such immediate
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43 increases in circulating IGF-1, because the response of IGF-1 to GH pulses is delayed (3-9
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45 hours) and peak values of IGF-1 may not be reached until after 16-28 hours post-exercise
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47 (Kraemer & Ratamess, 2005). In a study by Goto et al. (2003), the elevated GH levels after a
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49 combination of high and moderate intensity resistance training were correlated with the acute
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51 increases in thigh circumference. The acute increase in muscle CSA immediately post-
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53 exercise is in turn correlated with a decrease in plasma volume (Ploutz-Snyder et al., 1995).
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55 Plasma volume decreases of 20-22% have been noted after leg press and barbell squat
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3 exercises (Ploutz et al., 1993; Ploutz-Snyder et al., 1995). Therefore, the increase in IGF-1 in
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5 the study of Popov et al. (2006) may have been caused by hemoconcentration.
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9 Furthermore, the correlation between the acute increases in GH and IGF-1 reported in
10 the study of Popov et al. (2006) may be spurious, because of the relationship between acute
11 muscle volume changes and GH. The fluid shifts in resistance exercise from the circulation
12 into the active muscles are thought to be caused largely by accumulation of lactate, hydrogen
13 ions, sodium ions and phosphate in the working muscles (Ploutz-Snyder et al., 1995). These
14 metabolites and ions have also been implicated as important in the GH response to exercise,
15 presumably through metaboreceptors in the muscles that sense changes in concentrations and
16 provide feedback to the central nervous system (Gordon et al., 1994; Viru et al., 1998). Thus,
17 fatiguing low-to-moderate intensity strength training during ischemic conditions leads to
18 accumulation of metabolites and ions in the working muscles, which in turn leads to both an
19 increase in GH secretion (through feedback from muscle metaboreceptors) and increased
20 plasma levels of IGF-1 (mainly through hemoconcentration). Nevertheless,
21 hemoconcentration of hormones and growth factors may be of physiological significance as
22 increased blood concentration of these molecules, regardless of mechanism, means a greater
23 probability of interactions with receptors (Kraemer & Ratamess, 2005).
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44 Regarding longer-term changes in resistance training with vascular occlusion,
45 significant increases in circulating levels of IGF-1 along with gains in muscle volume were
46 reported in one study (Abe et al., 2005). However, it has been suggested that systemic factors
47 may be of secondary importance in muscle hypertrophy in comparison to the “local” system
48 of muscle adaptation (Adams, 2002b; Walker et al., 2004; Goldspink et al., 2006; Eliakim et
49 al., 2006). Still, this does not exclude the possibility that systemic factors may amplify the
50 hypertrophy induced by the localized training, as proposed by Viru & Viru (2000). Indeed, a
51 recent study on strength training with blood flow restriction (Madarama et al., 2008) provided
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3 evidence for a potentiating effect of systemic factors. In this study, performing additional leg
4 exercise with vascular occlusion after arm training resulted in greater increases in both muscle
5 area and isometric strength for the elbow flexors compared to an identical arm training regime
6 supplemented with leg exercise without occlusion.
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12 It is uncertain which factor(s) that could mediate this potentiating effect. In their paper,
13 Madarame et al. (2008) suggested that noradrenaline was responsible for the enhanced
14 hypertrophy, based on the differences in the acute response between the two regimes, while
15 GH and testosterone did not differ significantly. They also remarked that several beta-
16 adrenergic agonists have anabolic effects on skeletal muscle. However, a causative role for
17 catecholamines was not proven in their study. It should also be noted that the increase in GH
18 was significant for the occluded regime, while the response for the non-occluded regime was
19 not. Hence, a role for GH, either on its own or synergistically with the catecholamine
20 response, cannot be ruled out at present.
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34 However, numerous studies have demonstrated marked hypertrophy in response to
35 localised training regimes (for review, see Wernbom et al., 2007), and Walker et al. (2004)
36 reported equal gains in strength and muscle area in response to arm training only versus
37 combined arm and whole-body training. From their description, it appears that the arm
38 training routine in the study of Madarame et al. (2008) was submaximal in terms of the effort
39 required and the ~3-4% increase (not significant) in muscle area in the trained arm in the non-
40 occluded group compared to the ~11-12% increase in the occluded group suggests that it was
41 largely unsuccessful in itself. Therefore, it is presently unclear whether an additive effect of
42 an enhanced systemic response would occur in the presence of a more effective local training
43 stimulus. Furthermore, while the amplifying effect was present in the trained arm, the
44 untrained arm did not increase in muscle area (~1%). Thus, as the authors themselves noted, a
45 local exercise stimulus is indispensable for muscle hypertrophy.
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Local growth factors and intracellular signaling pathways

It is generally held that significant hypertrophy is seen only in the exercised muscle and not in other muscles in the body (Adams, 2002b; Goldspink et al., 2006). Several mechanisms intrinsic to the muscle are involved in the localized hypertrophic response to resistance training, including autocrine/paracrine growth factors, intracellular signaling induced by changes in the local environment (e.g. transduction of mechanical tension into intracellular signals), and changes in the content of receptors of hormones and growth factors.

IGF-1 is expressed in skeletal muscle in addition to being present in the circulation, which means that it can also act as a local growth factor. Changing the availability of the muscle growth factors IGF-1 and mechano growth factor (MGF, a splice variant of IGF-1) and myostatin appears to be a central regulatory process in adaptive skeletal muscle growth (Rennie et al., 2004). Localized infusion of IGF-1 or MGF as well as genetic overexpression of IGF-1 has been shown to increase muscle mass (reviewed by Goldspink et al., 2006) and increases in IGF-1 variants in skeletal muscle have been demonstrated in several animal and human models of functional overload, including resistance exercise (reviewed by Rennie et al., 2004; Glass, 2005; Tidball, 2005). Hypertrophic intracellular signaling downstream of IGF-1 include the phosphatidylinositol-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and the PI3K/Akt/glycogen synthase kinase 3 beta (GSK3 β) pathways (Rennie et al., 2004; Glass, 2005; Tidball, 2005). Akt is also known as protein kinase B (PKB). The downstream targets of the PI3K/Akt/mTOR pathway are the translational regulators p70S6 kinase (p70S6K) and eukaryotic initiation factor-4E binding protein (4E-BP), (Adams, 2002b; Rennie et al., 2004; Glass, 2005). Downstream in the PI3K/Akt/GSK3 β pathway is the eukaryotic initiation factor 2B (eIF2B). The end results of activation of these pathways are increases in protein synthesis and cell growth (Bolster et al., 2004; Glass, 2005).

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Contrary to the anabolic effects of IGF-1/MGF on skeletal muscle, myostatin acts as a negative regulator of skeletal muscle growth (Roth & Walsh, 2004). Increases in IGF-1/MGF have been observed after acute bouts and longer-term strength training (reviewed by Goldspink et al., 2006, see also Kim et al., 2005; Petrella et al., 2006). Reductions in myostatin have been noted in several (Roth et al., 2003; Walker et al., 2004; Kim et al., 2005; Petrella et al., 2006; Raue et al., 2006, Hulmi et al., 2007) but not all (e.g. Willoughby, 2004) studies on the myostatin response to strength training. Based on these observations, it has been hypothesised that the upregulation of IGF-1/MGF and the downregulation of myostatin are necessary for an optimal hypertrophic response (Kim et al., 2005).

Regarding any possible effects of occlusion training on local IGF-1/MGF in humans, there are at present no data available. There are also currently no reports concerning changes in myostatin in humans in conjunction with ischemic strength training. In a rat model of partial vascular occlusion, myostatin levels were shown to decrease along with increases in muscle weight and myofiber areas (Kawada & Ishii, 2005). Interestingly, no significant increase in the expression of IGF-1 was seen in this model. However, it should be noted that the model used by Kawada & Ishii (2005) involved chronic restriction of blood flow, as opposed to the intermittent occlusion models used in human studies and that this difference may result in substantially different adaptations.

The tension developed by the muscle appears to be a critical stimulus for the hypertrophy associated with strength training. Apart from acting via the induction of local growth factors such as IGF-1/MGF, it is becoming increasingly evident that mechanical tension can directly activate anabolic signaling pathways (reviewed by Vandeburgh 1992; Hornberger & Esser 2004; Huijing & Jaspers, 2005). It has been noted that the earliest activation of hypertrophic signaling after resistance exercise is too rapid to be accounted for by growth factors. Consequently, the involvement of mechanochemical transduction, and/or

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3 other processes such as calcium release, have been suggested in this early response, which is
4 followed by a late response presumably involving growth factors such as IGF-1/MGF (Rennie
5 & Wackerhage, 2003). Recently, it was observed that a functional IGF-1 receptor is not
6 necessary for overload-induced muscle hypertrophy in rats (Spangenburg et al., 2007); a
7 finding which strengthens the case for the importance of direct mechanotransduction. It is
8 beyond the scope of this paper to discuss the possible mechanisms by which tension is
9 transduced into intracellular signals, the interested reader is referred to the reviews above and
10 to recent original papers (Spangenburg & McBride, 2006; Boppart et al., 2006; Hornberger et
11 al., 2006). Interestingly, there appears to be some overlap between the pathways activated by
12 mechanical stimuli and those activated by growth factors (Tidball, 2005).
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27 In a recent study (Fujita et al., 2007), an acute bout of low intensity (20% of 1RM)
28 resistance training combined with vascular occlusion increased muscle protein synthesis,
29 along with an increase in the phosphorylation of p70S6K and a decreased phosphorylation of
30 eukaryotic elongation factor 2 (eEF2). These authors concluded that either hormonal changes,
31 metabolic stress and/or mechanotransduction signaling may have been involved in the
32 mTOR/p70S6K signaling. Because post-exercise biopsies were obtained only at a time point
33 of 3 hours after exercise, and no data on growth factor responses were reported, it is difficult
34 to assess the relative contributions of growth factors versus mechanotransduction and/or other
35 early events, including systemic responses, with this type of training.
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50 Other exercise-related factors

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55 Apart from hormones, growth factors and mechanical stimuli, a wealth of other factors in the
56 environment of the muscle also affect intracellular signaling. Changes in blood flow (Kraemer
57 & Ratamess, 2004), heat stress (Goto et al., 2003), reactive oxygen species (ROS) (Takarada
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3 et al., 2000a), hypoxia-hyperoxia (Kawada, 2005) and nitric oxide (NO) (Kawada & Ishii,
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6 2005) have all been suggested as possible stimuli in training with vascular occlusion.

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8 Blocking endogenous NO production decreases the hypertrophic response by ~50% in
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10 animal models of functional overload (Smith et al., 2002; Sellman et al., 2006). Furthermore,
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12 it has been demonstrated that satellite cells can be activated in response to mechanical stretch
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14 by the release of hepatocyte growth factor (HGF) in a NO-dependent manner (Tsatsumi et al.,
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16 2006). In addition, NO is involved in other mechanotransduction processes such as integrin
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18 signaling (Zhang et al., 2007). The isoforms of nitric oxide synthase (NOS) are activated by
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20 numerous stimuli, including exercise and possibly also hypoxia (Stamler & Meissner, 2001).
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25 In their study on a rat model of chronic partial occlusion, Kawada and Ishii (2005)
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27 reported increased levels of nitric oxide synthase 1 (NOS-1) mRNA along with the increase in
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29 muscle weight. However, changes in other possible regulators of muscle mass were also
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31 present, such as a decrease in myostatin and an increase in heat shock protein 72 (HSP-72).
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33 Little is currently known regarding the possible roles of NO in muscle hypertrophy in human
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35 models of resistance training, including ischemic strength training.
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40 It has been suggested that NO regulates the expression of cyclooxygenase 2 (COX-2) in
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42 skeletal muscle (Soltow et al., 2006). The COX enzymes catalyses the production of
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44 prostaglandins from arachidonic acid that is released from membrane phospholipids by the
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46 enzyme phospholipase A₂ (Bos et al., 2004; Shen et al., 2006). Prostaglandins of the COX-2
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48 pathway include prostaglandin E₂ (PGE₂) and prostaglandin F₂ alpha (PGF_{2α}). These were
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50 implicated in mechanotransduction and the control of protein synthesis and degradation
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52 already in the early 1980s (for review see Thompson & Palmer, 1998). Blocking the
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54 production of these prostaglandins blunts the increased protein synthesis after an acute bout of
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56 heavy eccentric exercise (Trappe et al., 2001; 2002). Furthermore, recent data suggest that the
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58 COX-2 pathway is important for myonuclear addition *in vivo* and satellite cell activation and
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3 proliferation in vitro (Bondesen et al., 2006) and $\text{PGF}_{2\alpha}$ may regulate hypertrophy of skeletal
4 muscle by activating both cell fusion and protein synthesis (Horsley and Pavlath, 2003).
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8 To date, no training study in humans has been published which has confirmed the role of
9 prostaglandins in skeletal muscle hypertrophy, but experiments with rodent models have
10 demonstrated the importance of the COX-2 pathway in recovery from atrophy (Bondesen et
11 al., 2006) and for hypertrophy resulting from functional overload (Soltow et al., 2006). Also,
12 a recent human study has shown increased levels of $\text{PGF}_{2\alpha}$ after conventional resistance
13 exercise (Trappe et al., 2006).
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22 Whether prostaglandins are produced in humans also in response to low load training
23 with vascular occlusion is currently not known. However, increased muscle levels of
24 arachidonic acid and prostaglandins have been noted in studies on cats subjected to
25 electrically induced isometric exercise and ischemia, and greater increases were seen after a
26 combination than after either intervention alone (Rotto et al., 1989; Symons et al., 1991).
27 Moreover, prostaglandins are involved in the sensitization and stimulation of group III and IV
28 muscle afferents, and the responses of these afferents are increased during dynamic exercise
29 with occlusion compared to freely perfused conditions (Hayes et al., 2006). Group IV thin
30 fibers represent the afferent pathway from metaboreceptors and may mediate the GH response
31 during muscle activity (Virus et al., 1998). On the basis of these observations, we suggest that
32 the potential role of prostaglandins in ischemic strength training should be investigated.
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48 Regarding the potential role of ROS in muscle hypertrophy, several interesting
49 observations have been made in both skeletal muscle and cardiac muscle. ROS have been
50 implicated in cardiac hypertrophy; an effect which may be mediated via phosphatidic acid,
51 which in turn is regulated by the enzyme phospholipase D (Tappia et al., 2006). In skeletal
52 muscle, recent evidence strongly suggests a role for phospholipase D activation and
53 subsequent production of phosphatidic acid in mTOR signaling in response to mechanical
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3 stimulation (Hornberger et al., 2006). In cardiac muscle, activation of phospholipase D is seen
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5 in the early part of the reperfusion after ischemia, whereas following prolonged reperfusion, a
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7 reduced activity is seen instead (Tappia et al., 2006). These authors speculated that low levels
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9 and brief exposures to ROS may stimulate phospholipase D-mediated signal transduction,
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11 whereas prolonged exposure and high levels of ROS result in phospholipase D inhibition. In
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13 line with these observations, low levels of hydrogen peroxide (H₂O₂) induces hypertrophy in
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15 cardiac myocytes, whereas higher concentrations result in apoptosis (Kwon et al., 2003).
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20 Concerning skeletal muscle, growing evidence support a role for ROS in muscle atrophy
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22 (reviewed by Powers et al., 2007), but again, this can possibly be explained by the negative
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24 effects of prolonged exposures and high levels of ROS, as opposed to brief exposures to low
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26 concentrations of ROS. Furthermore, H₂O₂ induces activation of p70S6K in different cell
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28 types (Bae et al., 1999; Tu et al., 2002) and it has been suggested that H₂O₂ acts as a second
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30 messenger in growth factor-induced p70S6K signaling (Bae et al., 1999). Given these
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32 findings, we suggest further studies on the possible involvement of ROS in mediating some of
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34 the hypertrophic adaptations to strength training during ischemic conditions.
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39 As argued by Widegren et al. (2001), it is unlikely that exercise responses are caused by
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41 one single mechanism and more likely that they depend on the integration of multiple local
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43 and systemic factors. As is obvious from the above discussion, numerous mechanisms may
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45 contribute to the hypertrophic effects seen after ischemic strength training. Current evidence
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47 suggests that the high degree of motor unit recruitment is a major factor, and there is also
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49 some data indicating that the systemic response may enhance the effects of the mechanical
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51 tension during certain circumstances (e.g. at low-to-moderate loads). The evidence for
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53 additive and/or independent effects of ischemia-reperfusion in the training situation, although
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55 an attractive hypothesis, is limited. Further investigations are obviously needed to study both
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57 the impact of individual factors and the interplay between them.
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Practical and health aspects

Is occlusion training safe and feasible?

As discussed by Takarada et al. (2000b), training with cuff occlusion may have the potential to create muscle damage and other serious side effects such as thrombosis and damage to blood vessels. Furthermore, high levels of ROS are linked to proteolysis and apoptosis (Powers et al., 2007). However, in another study by Takarada et al. (2000a), no evidence of muscle damage or high levels of oxidative stress were found as judged by the low levels of creatine kinase and lipid peroxide after their protocol. Although measurements of fiber areas have been included in a few studies (Ohta et al., 2003; Yasuda et al., 2005), little is currently known about the effects of occlusion training on soft tissues beneath and distal to the tourniquet, including markers of proteolysis, apoptosis and necrosis.

In our literature search, we found 13 training studies (see table 1 for references) using blood flow restriction with a tourniquet. These studies on occlusion training have typically lasted between 2 to 8 weeks but two studies (Takarada et al., 2000a; Ohta et al., 2003) lasted for 16 weeks. In these 13 studies, a total of 116 subjects trained a total of 4376 training sessions. In most of them, the occlusion was partial and the duration of occlusion generally lasted between 5-10 minutes and except for acute muscle pain, no adverse effects were reported. In a study by Kilian et al. (2005), 10 minutes of complete occlusion of the forearm resulted in no measurable effects on leukocyte and platelet activation and even 20 minutes of ischemia failed to result in measurable changes. Although some endothelial dysfunction was noted with especially the longer duration, this was essentially recovered within 60 minutes.

Recently, Nakajima et al. (2006) published a survey on the safety of occlusion training based on reports from 105 training centers in Japan, where this method, also termed “Kaatsu training”, has become widely popular for both fitness and rehabilitation purposes. A total of

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3 over 12600 individuals had trained using tourniquets in combination with different modes of
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5 exercise (walking, cycling, weight training, etc). The most common side effects were
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7 subcutaneous hemorrhage (incidence: 13.1%) and temporary numbness (1.3%). More serious
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9 side effects were rare: venous thrombosis (0.055%), deterioration of ischemic heart disease
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11 (0.016%), cerebral infarction (0.008%), rhabdomyolysis (0.008%) and pulmonary embolism
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13 (0.008%). It should be noted that this report was published by the same research group that
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15 has conducted most of the studies on this type of training. In summary, although current
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17 evidence suggests it may be a relatively safe mode of training in the short term, more research
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19 is needed regarding potential adverse effects and how these can be minimised.
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25 Aside from safety issues, the muscle pain experienced during ischemic strength training
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27 can be intense, and delayed onset muscle soreness (DOMS), is not uncommon (Wernbom et
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29 al., 2006). The DOMS subsides after a few workouts, suggesting a repeated bout effect, and it
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31 also appears that if the initial volume is low (e.g. 1-2 sets), much of the DOMS can be
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33 avoided (unpublished observations). Still, training combined with ischemia clearly requires a
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35 high degree of motivation from the trainee, especially if performed with a high level of effort.
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41 Narrow or wide tourniquets? 42 43 44

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46 A question which is of both practical and physiological relevance for training with pressure
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48 cuffs is the width of the tourniquet. In the context of limb surgery, it has been recommended
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50 that wide tourniquets should be used, since wide cuffs have been shown to achieve occlusion
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52 at considerably lower pressures than more narrow cuffs (Crenshaw et al., 1988; Graham et al.,
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54 1993). With wide tourniquets and lower pressures, the deleterious effects of high compression
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56 and shear forces on soft tissues may be reduced (Crenshaw et al., 1988; Graham et al., 1993).
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3 In most of the training studies published up to date, narrow cuffs have been used at
4 pressures of between 160 and 240 mm Hg. Takano et al. (2005) used a pressure of 160-180
5 mm Hg in combination with a 33 mm pressure belt and showed a reduction of femoral blood
6 flow to about 30% of normal resting conditions, before exercise. Immediately after exercise,
7 the blood flow was still markedly reduced to about 50% of that measured during rest. With a
8 140 mm wide cuff, Laurentino et al. (2008) reported cessation of the tibial artery pulse
9 (measured with Doppler) at pressures of ~130 mm Hg. Using a 135 mm wide curved
10 tourniquet with a 100 mm wide pneumatic bag inside of it, we have found that pressures of
11 ~90-110 mm Hg are usually sufficient to partially restrict blood flow and affect muscle
12 endurance (unpublished observations). Thus, it appears that high pressures during training are
13 not necessary with wide tourniquets and should probably be avoided because of potential risks
14 with the combination of severe occlusion and a high degree of compression.
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32 An obvious drawback with wide pressure cuffs is that they may interfere with the
33 exercise, but this is probably more significant when training the upper limb than the lower
34 limb. However, the upper limb requires less pressure to achieve occlusion and therefore the
35 tourniquets can be somewhat narrower. Even so, relatively wide cuffs of 70 to 90 mm in
36 width and relatively low pressures (100 mm Hg) have been applied in some experiments on
37 occlusion training for the elbow flexors (Takarada et al., 2000b; Moore et al., 2004). Another
38 potential drawback with wide cuffs is that more tissue gets compressed, but this is likely more
39 than outweighed by the reduction in shear forces and pressure gradients. Also, the
40 interindividual variability in the pressure needed to achieve complete occlusion is
41 considerably smaller with wide cuffs because the occlusion effect with these is much less
42 dependent on the circumference of the limb (Crenshaw et al., 1988). Translated to the training
43 situation, this should make it easier to find a proper pressure to achieve a partial occlusion.
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60 Taken together, it appears that relatively wide cuffs are preferable to narrow cuffs.

Are tourniquets necessary to induce relative ischemia with low-load training?

Studies investigating the static endurance of various muscle groups have shown that the difference in endurance between conditions of cuff occlusion and no occlusion disappears when the force level reaches ~40-60% of maximal voluntary isometric action (MVIA), (Bonde-Petersen et al., 1974; Hisaeda et al., 2001). This can be explained by the intramuscular occlusion of the blood flow which occurs due to the high pressure in the muscle (Sadomoto et al., 1983; Sejerstedt et al., 1984; Sjøgaard et al., 1988). Until recently, little data existed about the effects of cuff occlusion on endurance during conventional dynamic resistance training. Using a wide tourniquet and a pressure of 200 mm Hg during dynamic knee extension exercise with coupled concentric-eccentric actions, Wernbom et al. (2006) demonstrated significant differences in the number of repetitions performed between occluded and non-occluded conditions for loads of 20-40% of 1RM, but not for 50% of 1RM, when the exercise was performed continuously with no relaxation of the quadriceps. Thus, similarly to continuous isometric exercise, the application of a pressure cuff around the thigh appears to reduce knee extension endurance at low loads but not at moderate and heavier loads.

However, although the tourniquet affected the endurance at 20-40% of 1RM, these differences were minor at 30% and especially 40%. Furthermore, the subjects experienced ischemic pain in the working quadriceps even without a pressure cuff and at loads as low as 20% of 1RM. In support of these findings, Shoemaker et al. (1994) noted that the blood flow to the quadriceps was inadequate during continuous dynamic knee extension exercise at a load as low as 10% of MVIA. Further evidence that intramuscular restriction of blood flow can occur at low intensities was provided by de Ruiter et al. (2007), who showed that the oxygenation level in the vastus lateralis and medialis during isometric knee extensions reached values similar to total cuff occlusion already at torques of ~25% of MVIA.

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3 Muscle blood flow mainly occurs in the relaxation period between muscle actions
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5 (Bangsbo & Hellsten, 1998). Therefore, the dynamic knee extension, preferably in a cam-type
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7 machine with variable resistance, can be used to induce relative ischemia already at loads of
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9 ~20-30% of 1RM if performed in a non-stop manner to fatigue and with short rest periods
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11 (e.g. 15-45 s) between sets. Other quadriceps exercises can also be modified to achieve
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13 intramuscular restriction of blood flow. During closed kinetic chain exercises such as the
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15 squat and the leg press, the force demands of the movement dictate that the electrical activity
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17 of the quadriceps is high at flexed knee angles (90-100°) and low near full knee extension
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19 (Andersen et al., 2006). If the range of motion instead is limited to between ~50 and 100
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21 degrees of flexion, the muscle activity remains fairly high throughout the movement and
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23 intramuscular occlusion is thus more likely to occur.
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29 Several studies (Takarada & Ishii, 2002; Tanimoto & Ishii, 2005; Popov et al., 2006)
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31 have demonstrated muscle hypertrophy in the quadriceps as a result of conventional training
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33 with high work/rest ratios at intensities of ~50% of 1RM. Also, Laurentino et al. (2008) did
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35 not find any enhanced strength and hypertrophy in the quadriceps when cuff occlusion was
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37 added at training loads of ~60% and ~80% of 1RM. In our laboratories, we have noted high
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39 levels of muscle activity even without tourniquets at loads as low as 20-30% of 1RM in some
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41 exercises such as dynamic knee extensions, with the no-relaxation technique performed all-
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43 out to fatigue (manuscript in preparation). We therefore speculate that hypertrophy is possible
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45 without pressure cuffs even at these low intensities. In this context, it is noteworthy that in the
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47 occlusion training studies published to date, the groups that have trained without tourniquets
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49 have generally not trained to failure, whereas the occlusion groups have.
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55 Intuitively, a training model which is based on the muscles own internal restriction of
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57 blood flow would have advantages both from a safety point of view and from a practical point
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59 of view. On the other hand, in certain muscle groups and in some individuals, it may be
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3 difficult to induce relative ischemia at low loads by exercise alone, due to factors such as
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5 insufficient intramuscular pressures developed during exercise. Furthermore, it is possible that
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7 there are differences between the muscle ischemia resulting from exercise alone and the
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9 ischemia induced with a tourniquet in combination with exercise (e.g., a greater build-up of
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11 metabolites in the cuff-occluded muscle), which in turn could lead to differences in the
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13 stimulation of hypertrophic pathways. Future studies should compare the effects of ischemic
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15 training with and without cuff occlusion at the same level of effort.
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22 Dose-response aspects of ischemic training

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27 A strength training program can be described by a number of variables, the most important
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29 being frequency, intensity, volume and mode of training. Conventional heavy resistance
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31 training for the purpose of gaining muscle mass is usually performed for 2-3 sessions per
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33 week per muscle group and most rehabilitation programs aiming to restore muscle volume use
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35 similar training frequencies. A recent review (Wernbom et al., 2007) suggested that the
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37 average rate of gain for the quadriceps as a result of strength training for 2-3 sessions per
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39 week is on the order of ~0.11% increase in CSA per day. In the study of Abe et al. (2005), in
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41 which unusually rapid gains were noted (~0.55% increase per day on average), training was
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43 performed for 2 sessions per day, 6 days per week for a total of 12 sessions per week. This
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45 may seem like an extremely high frequency, but the authors speculated that because of the
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47 low mechanical stress (20% of 1RM) and little muscle damage, a much shorter recovery time
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49 between sessions was needed in comparison to conventional strength training. However,
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51 although the training included three sets of 15 repetitions, it is likely that the first two sets
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53 served to accumulate fatigue and that only the final set of each exercise was performed with a
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55 high level of effort. Furthermore, the training period was very short (two weeks) and the gains
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3 were markedly slower during the second week than the first. It is therefore uncertain whether
4 this frequency can be effective for longer periods or if overtraining would occur. From an
5 adherence point of view, such a high frequency is unrealistic for most people.
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10 Normal frequencies (2-3 times per week) have also been used with marked hypertrophy
11 of the quadriceps as a result (Takarada et al., 2002; Takarada et al., 2004; Kubo et al., 2006,
12 Madarame et al., 2008). The rates of hypertrophy observed in these four studies were between
13 0.04-0.22% per day (Table 1), which is within the range reported for conventional heavy
14 resistance training (0.03-0.26% per day) at similar frequencies (reviewed by Wernbom et al.,
15 2007). However, in these studies, multiple sets to failure or near were used. It is currently
16 unknown if multiple sets of fatiguing ischemic training is productive at higher frequencies
17 than 2-3 sessions per week. Equally unknown is whether low intensity ischemic strength
18 training in which only the final set is performed with a high degree of effort can induce
19 hypertrophy when performed for 2-3 sessions per week. At present, the interactions between
20 frequency, intensity and volume in ischemic strength training are not well understood.
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36 Not all modes of ischemic training are associated with increases in muscle strength
37 and/or marked increases in muscle protein content. Eiken et al. (1991) investigated the effects
38 of partial occlusion in a one-leg endurance cycling model and demonstrated an 8% decrease
39 in maximum peak torque after 4 weeks of training, 4 times per week for 45 minutes per
40 session. This occurred in spite of increased muscle fiber cross-sectional areas of both type I
41 and type II fibers in the ischemic leg in comparison to the normally trained leg. The authors
42 speculated that the decreased maximum strength in the ischemic leg was due to an increased
43 proportion of type I fibers that was evident in this leg after the training period compared to the
44 normal leg, suggesting that a fiber type shift had occurred. In a later study from the same
45 research group, increases in both mean fiber area (12%) and quadriceps muscle cross
46 sectional area (5%) were noted along with increased glycogen content in the ischemically
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3 trained muscles (Nygren et al., 2000). These authors then went on to investigate the effect of
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5 glycogen loading on muscle CSA and found that quadriceps muscle CSA increased with 3.5%
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7 when the subjects went from a glycogen depleted state to a loaded state during the course of
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9 four days (Nygren et al., 2001). These authors concluded that glycogen loading may
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11 contribute to the increase in muscle CSA seen after ischemic training. It should be noted that
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13 the increase in glycogen content as a result of glycogen loading from a depleted state was
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15 ~1.7 times larger than the increase seen after ischemic cycling.
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20 Taken together, it appears that ischemic endurance cycling, as performed in the studies
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22 of Eiken, Nygren and colleagues, leads to only minor increases in contractile protein content
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24 in the trained muscles. Interestingly, similar increases in glycogen content have been noted
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26 after ischemic strength training (Burgomaster et al., 2003). However, because significant
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28 strength gains are usually reported and because several studies have demonstrated gains in
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30 muscle CSA that have been substantially larger than ~3%, the contribution of increases in
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32 glycogen content to the hypertrophy seen after this type of training is probably minor.
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36 It is not immediately obvious why walk training with tourniquets (Abe et al., 2006)
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38 seems to be a better mode for inducing increases in both muscle strength and size than
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40 ischemic endurance cycling. Hypertrophy training is generally short-lasting and on the
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42 strength/power side of the strength-endurance continuum (Nader, 2005). Accordingly, it is
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44 possible that performing ischemic training in short intermittent working sets may cause the
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46 exercise-induced signaling to be more directed toward hypertrophic adaptations compared to
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48 longer continuous bouts. Also, longer ischemic bouts are associated with marked increases in
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50 plasma cortisol (Virus et al., 1998), which potentially cancel out some of the anabolic effects
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52 of the exercise. Differences in training frequency and/or the degree and pattern of ischemia-
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54 reperfusion may also contribute to the different results for walk training with tourniquets
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56 compared to ischemic cycle training.
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Low to moderate load ischemic training as an addition to heavy resistance exercise

In a series of studies, the group of Takamatsu and colleagues investigated the effects of adding fatiguing low to moderate intensity sets after high intensity sets on adaptations in muscle strength and size as well as on acute hormonal responses (Choi et al., 1998, Masuda et al., 1999; Goto et al, 2003a, b, 2004). Choi et al. (1998) demonstrated a high rate of increase in quadriceps muscle area after a regime where high intensity sets (70-80% of 1RM) were followed by sets to fatigue at succeeding lower loads (50-60% and of 40-50% of 1RM), with 30 second rest periods between the decrements in loads. Similar regimes of multiple sets to exhaustion with little or no rest between the decreasing loads are often performed by bodybuilders. Choi et al. (1998) and Masuda et al. (1999) also showed that this type of regime resulted in greater increases in whole muscle area and muscle fiber area compared to a pure high intensity (90% of 1RM) routine.

Goto et al. (2003a, 2004) investigated the effects of adding a single moderate intensity (50% of 1RM) set performed to failure after multiple high intensity (90% of 1RM) sets and found both larger acute increases in GH and greater increases in quadriceps muscle CSA and strength over time compared to performing only high intensity sets. Goto et al. (2004) speculated that the greater GH response seen with the combined regime could be an important factor, but also acknowledged that the increased volume of work may have provided a stronger stimulus for muscle hypertrophy. In addition, it is possible that some local mechanisms were enhanced due to the more sustained ischemia (e.g. greater production of prostaglandins and/or phosphatidic acid in the working muscles). Because of the relatively few studies that have been performed to date on combined or hybrid regimes, further research is obviously needed to establish whether low to moderate-intensity ischemic training has an additive effect also when added to an already very effective high-intensity routine.

Potential disadvantages of low-load ischemic training compared with conventional heavy resistance training

Training with lighter loads implicates that compression forces on bones and joints as well as strain on tendons are reduced compared to traditional strength training. In the late 1800's, it was observed that bone architecture adapts to mechanical loading so that the trabecular patterns coincide with the trajectories of the mechanical stresses (Wolff 1892, translated by Maquet and Furlong, 1986). Later workers have extended this concept and proposed that bone strength adapts chiefly to peak momentary loads (Frost, 2001). In support, cross-sectional studies of different types of athletes have demonstrated that adaptations in bone mineral density (BMD) are load-dependent (e.g. Nevill et al., 2004). Similarly, longitudinal studies have shown that increases in bone mineral density are greater after maximal eccentric training than maximal concentric training (Hawkins et al., 1999) and after high-load conventional strength training compared with moderate-load training (Kerr et al., 1996). Consequently, it is reasonable to assume that light-resistance occlusion training has less impact on bone metabolism than traditional high-load strength training. However, training with vascular occlusion can increase markers of bone turnover (Beekley et al., 2005), so it remains to be shown how this type of training affects bones over time and if it is a useful tool in the prevention of bone mineral loss in various situations of inactivity.

The adaptations of tendons to training vary with the mode of exercise performed (e.g., Kubo et al., 2001; Simonsen et al., 1995) and high resistance training seems to increase stiffness of human tendons (Kubo et al., 2001; Reeves et al., 2003; Kongsgaard et al., 2007). In a recent study by Kubo et al. (2006), young males trained one leg with high load (80% of 1RM) dynamic knee extensions and the other with low load (20% of 1RM) knee extensions under conditions of vascular occlusion. After 12 weeks of training, both protocols resulted in

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3 significant increases in muscle strength, and the gains in muscle volume of the quadriceps
4 femoris were similar for the two limbs. However, only the high load protocol significantly
5 increased stiffness in the tendon-aponeurosis complex. Furthermore, only the leg that had
6 been trained with the high load protocol showed increases in EMG, muscle activation and
7 specific tension. In support of the importance of load or strain magnitude, Arampatzis et al.
8 (2007) reported increased Achilles tendon stiffness and CSA after 14 weeks of training with
9 isometric contractions at 90% of MVC, whereas isometric contractions at 55% of MVC had
10 no effect on the tendon stiffness or CSA. In summary, it seems reasonable to suggest that
11 while the effects of blood flow-restricted training at low loads and traditional heavy-resistance
12 training on muscle volume are similar, the effects of low-load ischemic training on tendons,
13 and possibly also on neural adaptations, are less than with conventional strength training.
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32 **Perspectives**

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36 The research on resistance exercise performed during ischemic conditions has so far provided
37 important new insights into the physiology of strength training. In addition to being a possible
38 alternative or complement to conventional high-load resistance training in certain situations,
39 ischemic strength training may also have a place in sports training. Because relative ischemia
40 can be induced at rather low loads in certain exercises even without tourniquets, external
41 pressure may not always be necessary to achieve significant training effects. Also, any unique
42 effects of cuff occlusion *per se* during exercise have yet to be determined because the
43 increased training effects observed in the studies published to date may simply have been due
44 to greater effort. With reference to training combined with cuff occlusion, current evidence
45 suggests that this mode of exercise is relatively safe, but more research is needed especially
46 regarding the potential adverse effects on soft tissues.
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Table 1. Studies examining training effects of resistance exercise combined with vascular occlusion.

Reference	Gender, No of subjects	Age	Training status	Training-methods	Exercise(s)	Intensity (% of 1RM)	Sets	Reps	Rest between sets	Frequency (sessions/week)	Period length (days)	Change in muscle strength (%)	Change in muscle size (% CSA)	% change per day, method	Comments
Shinohara et al (1998)	Male (5)	23 (19-29)	Untrained	Isometric (+vascular occlusion)	Knee-extension (unilateral)	40% of MVC	1	~36		3	28	+26% (MVC)	-	-	Continuous severe occlusion, >250 mm Hg, cuff width not reported. Intermittent exercise, 2 s duration with 3 s rest between.
				Isometric	Knee-extension (unilateral)	40% of MVC	1	~36		3	28	+9% (MVC)	-	-	Contralateral leg which was trained as above but without occlusion.
Takarada et al (2000)	Female (11)	58±2	Untrained	Conc+Ecc Weight resistance (+VO)	Elbow flexion (unilateral)	53%	3	~18	60 s	2	112	+18.4% (average of torques, -90 to 90°/s)	+20.3 (biceps)	+0.22 (MRI)	Continuous partial occlusion. Cuff width = 33 mm, cuff pressure ~110 mm Hg. Training to failure in each set.
				Conc+Ecc (WR)	Elbow flexion (unilateral)	76%	3	~19	60 s	2	112	+22.6% (average of torques, -90 to 90°/s)	+18.4 (biceps)	+0.16 (MRI)	Contralateral arm trained at high intensity without occlusion. Training to failure in each set.
	F (8)	57±2	Untrained	Conc+Ecc (WR)	Elbow flexion (unilateral)	54%	3	~18	60 s	2	112	+1.0% (average of torques, -90 to 90°/s)	+6.9 (biceps)	+0.06 (MRI)	Group that trained at the same relative intensity and volume but without occlusion.
Takarada et al (2002)	M (6)	25±1	Strength-trained rugby-players	Conc+Ecc (WR +VO)	Knee-extension (bilateral)	50%	5	~16	30 s	2	56	+14.3% (average of torques, 0 to 180°/s)	+12.3 (quadriceps)	+0.22 (MRI)	Continuous partial occlusion. Cuff width = 33 mm, cuff pressure ~196 mm Hg. Training to failure in each set.
	M (5)	26±1	Strength-trained rugby-players	Conc+Ecc (WR)	Knee-extension (bilateral)	50%	5	~16	30 s	2	56	+3.2% (average of torques, 0 to 180°/s)	-	-	Group that trained at the same relative intensity and volume but without occlusion.

Table 1. (Continued)

Reference	Gender, No of subjects	Age	Training status	Training-methods	Exercise(s)	Intensity (% of 1RM)	Sets	Reps	Rest between sets	Frequency (sessions/week)	Period length (days)	Change in muscle strength (%)	Change in muscle size (% CSA)	% change per day, method	Comments
Burgomaster et al (2003, Moore et al (2004))	M (8)	20±0	Untrained	Conc+Ecc (WR+VO)	Elbow flexion (unilateral)	~50%	3-6	~5-10	60 s	2	56	+10.5 (concentric torque 60°/s) +23 (1RM) +10 (MVC)	-	-	Continuous partial occlusion. Cuff width = 70 mm, cuff pressure ~100 mm Hg. 5minutes rest between set 3 & 4. Training to failure in most of the sets.
				Conc+Ecc (WR)	Elbow flexion (unilateral)	~50%	3-6	~5-10	60 s	2	56	+9.6% (concentric torque 60°/s) +23 (1RM) +0 (MVC)	-	-	Contralateral arm which was trained without occlusion. Number of repetitions was matched to that of the occluded arm.
Takarada et al (2004)	M (6)	21±1	Physically active	Conc+Ecc (WR+VO)	Knee-extension (bilateral)	16-22%	5	15-23	60 s	2	56	+9.2% (average of torques, 0 to 180°/s)	+10.3	+0.18 (MRI)	Continuous partial occlusion. Cuff width = 90 mm, cuff pressure ~218 mm Hg. Training to failure in each set.
	M (6)	22±1	Physically active	Conc+Ecc (WR)	Knee-extension (bilateral)	16-22%	5	15-23	60 s	2	56	+3.1% (average of torques, 0 to 180°/s)	+1	+0.02 (MRI)	Group that trained at the same relative intensity but without occlusion.
Abe et al (2005a)	M (9)	24±8	Physically active	Conc+Ecc (WR+VO)	Squat (machine)	20%	3	15	30 s	12 (6 days, 2x/d)	14	+16.8% (1RM)	+8.0 (quadriceps) +8.0 (adductors) +9.1 (gluteus maximus)	+0.57 (MRI) +0.57 +0.65	Continuous partial occlusion. Narrow cuff, width not reported. Pressure increased from ~160 to 240 mm Hg during the training period.
				Conc+Ecc (WR+VO)	Knee flexion	20%	3	15	30 s	12 (6 days, 2x/d)	14	+22.6% (1RM)	+10.7% (hamstrings)	+0.76 (MRI)	

Table 1. (Continued)

Reference	Gender, No of subjects	Age	Training status	Training-methods	Exercise(s)	Intensity (% of 1RM)	Sets	Reps	Rest between sets	Frequency (sessions/week)	Period length (days)	Change in muscle strength (%)	Change in muscle size (% CSA)	% change per day, method	Comments
Abe et al (2005a) (continued)	M (7)	24±8	Physically active	Conc+Ecc (WR)	Squat (machine)	20%	3	15	30 s	12 (6 days, 2x/d)	14	+8.9% (1RM)	+1.8 (quadriceps) +0.2 (adductors) +1.4 (gluteus maximus)	+0.13 (MRI) +0.01 +0.10	Group that trained at the same relative intensity but without occlusion.
				Conc+Ecc (WR)	Knee flexion	20%	3	15	30 s	12 (6 days, 2x/d)	14	+1.3% (1RM)	+1.5% (hamstrings)	+0.11 (MRI)	
Abe et al (2005b)	M (9)	-	Track and field athletes	Conc+Ecc (WR+VO)	Squat (machine)	20%	3	15	30 s	14 (7 days, 2x/d)	8	+9.6% (1RM)	+5.9 (quadriceps thickness)	+0.74 (UL)	Continuous partial occlusion. Narrow cuff, width not reported.
				Conc+Ecc (WR+VO)	Knee flexion	20%	3	15	30 s	12 (7 days, 2x/d)	8	-	+4.5% (hamstrings thickness)	+0.56 (UL)	Pressure increased from ~160 to 240 mm Hg during the training period.
	M (6)	-	Track and field athletes	Conc+Ecc (WR)	Squat (machine)	20%	3	15	30 s	14 (7 days, 2x/d)	8	+4.8% (1RM)	±0 (quadriceps thickness)	±0 (UL)	Group that trained at same relative intensity but without occlusion.
				Conc+Ecc (WR)	Knee flexion	20%	3	15	30 s	14 (7 days, 2x/d)	8	-	±0 (hamstrings thickness)	±0 (UL)	
Kubo et al (2006)	M (9)	25±2	-	Conc+Ecc (WR+VO)	Knee-extension (unilateral)	20%	4	12-25	30 s	3	84	+7.8% (MVC)	+5.9 (quadriceps volume)	+0.07	Continuous partial occlusion. Narrow cuff, width not reported. Cuff pressure increased from ~180 to 240 mm Hg during the training period.
				Conc+Ecc (WR)	Knee-extension (unilateral)	80%	4	10	60 s	3	84	+16.8% (MVC)	+7.4 (quadriceps volume)	+0.09	Contralateral leg which was trained without occlusion and at heavier loads.

Table 1. (Continued)

Reference	Gender, No of subjects	Age	Training status	Training-methods	Exercise(s)	Intensity (% of 1RM)	Sets	Reps	Rest between sets	Frequency (sessions/ week)	Period length (days)	Change in muscle strength (%)	Change in muscle size (% CSA)	% change per day, method	Comments
Madarama et al (2008)	M (8)	22±2	Untrained	Conc+Ecc (WR+VO)	Knee ext. (bilateral)	30%	3	15-30	30 s	2	70	+19.6% (MVC)	+4.3 (quadriceps)	+0.06 (MRI)	Continuous partial occlusion. Cuff width = 40 mm. Cuff pressure increased from ~160 to 240 mm Hg during the training period.
				Conc+Ecc (WR+VO)	Knee flex. (bilateral)	30%	3	15-30	30 s	2	70	+18.3% (MVC)	+5.7% (hamstrings)	+0.08 (MRI)	
				Conc+Ecc (WR)	Elbow flexion (unilateral)	50%	3	10	180 s	2	70	+9.0% (MVC)	+11.5% (elbow flexors)	+0.16 (MRI)	
	M (7)	22±4	Untrained	Conc+Ecc (WR)	Knee ext. (bilateral)	30%	3	15-30	30 s	2	70	+4.6% (MVC)	-1.3 (quadriceps)	-0.02 (MRI)	Group that trained without occlusion.
				Conc+Ecc (WR)	Knee flex. (bilateral)	30%	3	15-30	30 s	2	70	+2.9% (MVC)	+0.3% (hamstrings)	+0.00 (MRI)	
				Conc+Ecc (WR)	Elbow flexion (unilateral)	50%	3	10	180 s	2	70	+3.5% (MVC)	+3.5% (elbow flexors)	+0.05 (MRI)	
Laurentino et al (2008)	M (8)	24±3	Physically active	Conc+Ecc (WR+VO)	Knee ext. (unilateral)	~80%	3-4	6	120 s	2	56	+34.5% (1RM)	+5.0 (quadriceps)	+0.09 (MRI)	Intermittent occlusion. Cuff width = 140 mm. Cuff pressure = 126 mm Hg. Training to failure in each set.
				Conc+Ecc (WR)	Knee ext. (unilateral)	~80%	3-4	6	120 s	2	56	+36.9% (1RM)	+6.1 (quadriceps)	+0.11 (MRI)	
	M (8)	22±3	Physically active	Conc+Ecc (WR+VO)	Knee ext. (bilateral)	30%	3-4	12	120 s	2	56	+35.3% (1RM)	+4.5 (quadriceps)	+0.08 (MRI)	Intermittent occlusion. Cuff width = 140 mm. Cuff pressure = 131 mm Hg. Training to failure in each set.
				Conc+Ecc (WR)	Knee ext. (unilateral)	80%	3-4	12	120 s	2	56	+37.6% (MVC)	+3.2 (quadriceps)	+0.06 (MRI)	

1 Note: the studies of Ohta et al (2003), Ishii et al (2005) and Teramoto & Golding (2006) are not included in this table, because it was not possible to quantify
2 the exercise intensities in relative terms from the descriptions of their training programs. The study of Yasuda et al (2005) was based on subjects from the
3 study of Abe et al (2005a) and is therefore not included in this table. Abbreviations: 1RM = one repetition maximum. Con = concentric. CSA = cross
4 sectional area. Ecc = eccentric. MRI = magnetic resonance imaging. MVC = maximal voluntary (isometric) contraction. Reps = repetitions. UL = ultrasound.
5 VO = vascular occlusion. WR = weight based resistance.
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