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Review

Potential safety issues with blood flow restriction training

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The focal point of previous literature was establishing the efficacy of blood flow restriction training with respect to muscular strength, muscular hypertrophy, and muscular endurance. After mounting evidence supporting the efficacy of low-intensity blood flow restriction training, research has shifted to the overall safety of this training modality. The aim of this review was to summarize the research on the overall safety of blood flow restriction training, focusing on the cardiovascular system (central and peripheral), muscle damage, oxidative stress, and nerve conduction velocity responses compared with those observed with regular exercise. Although still sparse, the blood flow restriction training research thus far is promising with respect to safety outcomes. Individuals respond similarly to blood flow restriction training and to regular exercise; however, longer term studies are required to better understand the chronic effects of low-intensity blood flow restriction training and possible safety issues.

The American College of Sports Medicine (ACSM) recommends weight training at 70% or greater of one's one repetition maximum (1RM) in order to achieve muscular hypertrophy under normal conditions. Exercise intensities below 70% 1RM rarely produce substantial muscle hypertrophy or strength gains (ACSM, 2009). However, many individuals such as the elderly and rehabilitating athletes are unable to withstand the high mechanical stresses placed upon the joints during heavy resistance training; therefore, professionals have sought lower intensity training alternatives.

One such alternative is training with low intensities in combination with blood flow restriction, also known as KAATSU training. Blood flow restriction training, as the name implies, involves decreasing blood flow to a muscle by application of a wrapping device, such as a blood pressure cuff or specially designed restrictive straps. Evidence indicates that this style of training can provide a unique, beneficial mode of exercise, even in clinical settings, because it produces positive training adaptations equivalent to the physical activity of daily life (10–30% of maximal work capacity) (Abe et al., 2006). Muscle hypertrophy has recently been shown to occur even during exercise with intensities as low as 20% 1RM with moderate vascular restriction ($\sim$ 100 mmHg) (Yasuda et al., 2005), which could be quite beneficial to athletes (Takarada et al., 2000a) and patients in post-operation rehabilitation, particularly those with ACL injuries (Takarada et al., 2000b; Ohta et al., 2003), the elderly (Fry et al., 2010; Karabulut et al., 2010), and even astronauts (Iida et al., 2007; Loenneke & Pujol, 2010). Published studies hypothesize that blood flow restriction training induces skeletal muscle hypertrophy through a variety of mechanisms (for a review, please see (Loenneke et al., 2010); however, a definitive mechanism has yet to be elucidated.

The focal point of previous literature was establishing the efficacy of blood flow restriction training with respect to muscular strength, muscular hypertrophy, and muscular endurance (for reviews, please see (Wernbom et al., 2008; Loenneke & Pujol, 2009, 2010; Manini & Clark, 2009; Loenneke et al., 2010). After demonstrating the efficacy of blood flow restriction training, the literature now has shifted more toward the overall safety issues of training with moderately restricted blood flow (Clark et al., 2010; Madarame et al., 2010; Renzi et al., 2010). Therefore, the purpose of this manuscript is to provide an updated review on several measures of safety with respect to blood flow restriction training, and compare those responses to regular exercise.

Cardiovascular

Peripheral blood flow changes

Because blood flow dynamics are manipulated with blood flow restriction training, there are obvious potential safety concerns for practitioners with respect to blood flow changes post-exercise (PO_{bf}). The congestion and distension of veins that can occur from the pooling of blood with blood flow restriction could potentially result in valve damage within the veins. The cardiovascular responses to regular exercise are partially dependent upon the type of muscle contraction, with differing intensities and types of contraction (isometric, dynamic, eccentric, etc.) producing different patterns of blood flow. Alomari and Welsch (2007) reported increased peak PO_{bf} with dynamic handgrip exercise; however, others have reported decreased PO_{bf} follwing isometric contractions (McGowan et al., 2006, 2007).

Studies investigating PO_{bf} following blood flow restriction exercise are sparse. Renzi et al. (2010) reported decreased flow-mediated vasodilation following 14 min of blood flow restriction walking. In contrast to this acute study, Patterson and Ferguson (2010) reported that chronic (4 weeks) plantar flexion exercise with blood flow restriction resulted in an enhanced PO_{bf} compared with resistance exercise alone, suggesting that the blood flow with restrictive exercise is acutely impaired post-exercise but enhanced over repeated bouts of exercise.

The exact mechanism for the increase in PO_{bf} with chronic blood flow restriction exercise remains unknown. Patterson and Ferguson (2010) postulated that perhaps an increased venous compliance from the pooling of blood associated with blood flow restriction training could explain the increase in PO_{bf} (Convertino et al., 1988). Other potential explanations include the restriction of oxygen and/or accumulation of metabolites, specifically vasoactive metabolites (e.g. adenosine) (Loenneke et al., 2010). The accumulation of metabolites and the decreased availability of oxygen results in the recruitment of fast twitch (FT) fibers at lower than expected exercise intensities (Loenneke et al., 2010). FT fibers have demonstrated preferential capillarization compared with slow twitch fibers in certain situations (Adair et al., 1990). Local metabolic changes may also play an important signaling role for vascular endothelial growth factor (VEGF) upregulation (Roca et al., 1998), possibly initiated through the VEGF/NO cascade (Milkiewicz et al., 2005), because at least one study reported VEGF increased in response to resistance training with blood flow restriction (Takano et al., 2005). Additionally, capillary shear stress facilitates angiogenesis, thus reperfusion of blood flow post-exercise might also contribute to the enhancement of blood flow following blood flow restriction exercise (Suzuki et al., 2000; Hudlicka & Brown, 2009). Further support comes from Evans et al. (2010) who recently reported that 4 weeks of blood flow restriction exercise (plantar flexion) enhanced microvascular filtration, an index of capillarity, supporting the hypothesis that an increase in capillarization can occur.

Like PO_{bf}, research is equivocal regarding the changes in peripheral pulse wave velocity (PWV) from regular exercise. PWV is an indirect measure of peripheral arterial stiffness, determined by measuring waveforms from the common femoral and posterior tibial artery of the ankle (Clark et al., 2010). PWV increases as arterial stiffness increases. Collier et al. (2008) found that 4 weeks of resistance training (65% 1RM) increased peripheral PWV; however, several studies have shown no deliterious effect of resistance training on arterial stiffness (PWV) (Cortez-Cooper et al., 2005; Casey et al., 2007; Yoshizawa et al., 2009). The Collier et al. (2008) study investigated pre- and stage 1 hypertensive patients, which might explain the disparity in findings (elevated sympathetic outflow). Clark et al. (2010) found no changes in PWV following 4 weeks of bilateral knee extensor training with either low-intensity blood flow restriction training (30% 1RM) or high-intensity exercise (80% 1RM).

Other indices of peripheral resistance, total peripheral resistance (TPR) and ankle brachial index (ABI), have also been investigated with blood flow restriction training. Takano et al. (2005) found peak TPR to be similar between blood flow restricition exercise and a work matched control group; however, more recently, Renzi et al. (2010) found TPR to be significantly higher (BFR = $\sim$ 12% vs CON = $\sim$ 40%) during walking with blood flow restriction. These different intensities might be attributable to the different exercise modes or the overall volume of exercise. ABI appears to remain unchanged following both acute (Renzi et al., 2010) and chronic blood flow restriction exercise (Clark et al., 2010).

In summation, the peripheral blood flow response to blood flow restriction training appears to respond in a similar fashion as regular exercise, and future research efforts might be better served to focus on the time course of the PO_{bf} impairment observed with acute blood flow restriction exercise. In addition, chronic blood flow restriction training studies should be designed to measure both the chronic effects of training, as well as the acute responses observed on the last training day of a program, and the exercise should include more than one muscle group being trained in a session in order to better reflect a real-world setting.

Central responses of the cardiovascular system

In general, dynamic exercise results in a simultaneous decrease in peripheral resistance with a concomitant increase in heart rate and stroke volume (Mayo & Kravitz, 1999). These responses result in only slight increases in mean arterial pressure (MAP). During high-intensity double leg resistance training, based on ACSM guidelines (70–100% 1RM), there is complete occlusion of the skeletal muscle vasculature from mechanical compression and increases in intrathoracic pressure. Extensive research from MacDougall's lab using a high-intensity (80–100% 1RM) double leg press model demonstrated peak systolic and diastolic pressures as high as 480/350 mmHg and a doubling of MAP (114–212 mmHg) (MacDougall et al., 1985, 1992; Haslam et al., 1988; Lentini et al., 1993). Additionally, heart rates reached values of 170 beats per minute or higher. End-diastolic and end-systolic volumes declined by 30% and 50%, respectively, with a concomitant 17–35 mL decline in stroke volume. In comparison with low-intensity non-occlusion exercise (20% 1RM), low-intensity blood flow restriction training (20% 1RM) with the lower body (bilateral leg extensions) has been found to result in slightly greater values for heart rate (109 vs 96 bpm), and systolic (182 vs 155 mmHg), diastolic (105 vs 99 mmHg), and mean arterial blood pressures (127 vs 113 mmHg) (Takano et al., 2005); however, these values are all well below changes that occur during high-intensity resistance training. While end-diastolic and end-systolic volumes have yet to be measured with blood flow restriction training, slight declines in stroke volume (12%), but not cardiac output, have been observed with blood flow restriction training (Takano et al., 2005). Because these central cardiovascular responses are generally lower than traditional resistance training, they suggest that low-intensity blood flow restriction training is a safe alternative.

It should be noted that although Takano et al. (2005) observed central cardiovascular values lower than traditional resistance training studies, different exercises were used. Central cardiovascular responses to double leg press with blood flow restriction have yet to be investigated. In addition, although traditional resistance training results in acute spikes in blood pressure, research has observed a beneficial post-exercise hypotensive response (MacDonald et al., 1999; Fisher, 2001; Simao et al., 2005; de Salles et al., 2010), even observed at intensities as low as 50% 1RM (Fisher, 2001). Furthermore, evidence exists to indicate that chronic traditional resistance training might also lower resting blood pressure (Cornelissen & Fagard, 2005). Future blood flow restriction research should investigate the post-exercise blood pressure response into recovery as well as the effect of chronic training on resting blood pressure.

Blood coagulation

Hemostasis is maintained through a balance between coagulation and fibrinolytic activity and exercise has been shown to affect activation of both processes (Nakajima et al., 2007). Regular exercise preferentially activates fibrinolysis, while strenuous exercise may increase activity of the coagulation system, resulting in venous thrombosis. Research demonstrates that complete vascular occlusion can cause the formation of a thrombus and can induce a microvascular occlusion even after reperfusion. This post-reperfusion occlusion can result in both muscle damage and cell necrosis (Harman, 1948; Strock & Majno, 1969). Furthermore, the literature has suggested that metabolic and/or adrenergic factors may play some role in exercise-induced thrombin production. To illustrate, Herren et al. (1992) reported a positive correlation between post-exercise blood lactate and thrombin–antithrombin III complex (TAT) concentrations and Wallen et al. (1999) found that an adrenaline infusion, as well as fatiguing exercise, also increased plasma TAT.

Nakajima et al. (2006) first investigated the question of thrombosis in a survey of Asian facilities implementing blood flow restriction training. Only 0.06% out of 300 000 training sessions resulted in an incidence of venous thrombosis, which is lower rate than that reported for the general Asian population ($\sim$ 0.2–0.26%) (Klatsky et al., 2000). Nakajima confirmed their survey findings with a study measuring various blood markers such as D-dimer and fibrin degradation product (FDP), markers of intravascular clot formation, which were not increased following low-intensity blood flow restriction exercise (30% 1RM). Prothrombin time (PT) and thrombin time, markers of coagulation activity, were also unaffected with low-intensity blood flow restriction exercise. However, blood flow restriction training did result in increased tissue plasminogen activity (tPA), a fibrinolytic protein that catalyzes the conversion of plasminogen to plasmin, without affecting plasminogen activator of inhibitor-1, the principle inhibitor of tPA (Nakajima et al., 2007).

Clark et al. (2010) further investigated the coagulation effects of blood flow restriction exercise and found that neither PT nor D-dimer increased acutely or chronically following 4 weeks of low-intensity blood flow restriction training (30% 1RM) in 20–30 year olds. Fry et al. (2010) also found that D-dimer was unaffected in elderly subjects (70 years of age) performing an acute blood flow restriction exercise bout (20% 1RM). However, one study (Zaar et al., 2009) found that plasma TAT, a marker of thrombin generation, increased after a 10 min bout of lower body negative pressure at 30 mmHg, despite plasma D-dimer not increasing (Zaar et al., 2009). To

address this concern, Madarame et al. (2010) investigated all previous blood markers of the coagulation system as well as TAT, and reported that neither markers of intravascular clot formation (D-dimer, FDP) nor TAT were increased with low-intensity blood flow restriction exercise (30% 1RM).

In summation, coagulation activity does not appear to increase following low-intensity blood flow restriction exercise. In contrast, fibrinolytic potential (tPA) appears to be enhanced with blood flow restriction exercise as it is with traditional resistance training. Protocols that have investigated coagulation activity have implemented cuff sizes ranging from 50 to 60 mm, restriction pressures of 150–200 mmHg and exercise intensities ranging from 20% to 30% 1RM for up to four sets of lower body exercise ($\sim$ 10–15 min total time under restriction) (Nakajima et al., 2007; Clark et al., 2010; Fry et al., 2010; Madarame et al., 2010). Thus, these findings are specific to studies using similar protocols and are not necessarily applicable to all blood flow restriction training models. Interestingly, vascular compressions alone have long been associated with an increase in fibrinolytic activity without elevation of the coagulation cascade (Holemans, 1963; Robertson et al., 1972; Shaper et al., 1975; Stegnar & Pentek, 1993). Thus, it is currently unknown if the fibrinolytic response is from the exercise bout, the moderate restriction stimulus, or the combination of both. Future research should examine what effects longer duration low-intensity blood flow restriction exercise might have on the coagulation system.

Oxidative stress

Oxidative stress is a biological phenomenon marked by an imbalance between reactive free radicals and antioxidant defenses (Halliwell & Gutteridge, 1999). The term oxidative stress indicates a combination of increased free radical production and/or exhaustion of antioxidant defenses (local water-soluble than fat-soluble antioxidants). Severe acute or prolonged chronic oxidative stress can lead to oxidatively modified lipids, proteins, and DNA (Hudson et al., 2008).

An acute exercise bout under normal conditions is typically associated with a transient increase in oxidative stress, with the response being proportional to exercise intensity. The literature demonstrates that high-intensity exercise ($\geq$ 70% 1RM) involving a large muscle mass consistently elicits a measurable increase in blood oxidative stress markers (Lee et al., 2002; Bloomer et al., 2005, 2006, 2007; Hudson et al., 2008), but the responses to lower intensity resistance exercise ($<$60% 1RM) have been mixed (McBride et al., 1998; McAnulty et al., 2005). Not only is the oxidative stress response affected by exercise intensity, it has also been shown to increase with ischemic reperfusion (IR) models (Tsutsumi et al., 2007). IR in muscle results in an increased vascular permeability, attributed to an increase of xanthine oxidase activity during the hypoxic condition resulting in elevated reactive oxygen species (ROS) (Korthuis et al., 1985).

Although IR models increase ROS levels, this has not been observed with exercise in combination with moderate vascular restriction. Takarada et al. (2000a) provided the first study looking at oxidative stress following low-intensity (20% 1RM) knee extensor exercise with moderate blood flow restriction ($\sim$ 214 mmHg). Using thiobarbituric acid reactive substances (TBARS) as the measure, Takarada et al. (2000a) found no increases in TBARS with either low-intensity exercise or low-intensity exercise with blood flow restriction (20% 1RM). One limitation of this study was the measurement of TBARS, which is a non-specific and insensitive measure of lipid peroxidation. To address this, Goldfarb et al. (2008) followed up with a study measuring protein carbonyls and blood glutathione status, both of which are sensitive indicators of oxidative stress. They found that neither was increased with low-intensity blood flow restriction exercise (30% 1RM); however, elevations were seen with the moderate resistance exercise ($\sim$ 70% 1RM) and during blood flow restriction without exercise.

Goldfarb et al. (2008) cited two possible explanations for why oxidative stress remained unchanged with respect to blood flow restriction and exercise. The first possibility is that the muscle contractions during the partial occlusion were able to overcome the resistance to venous outflow and thus helped remove the oxidative stress markers from the circulation. The second possibility is that the pressures during the contractions were sufficient to enhance blood flow during the muscle contractions, which enabled adequate blood flow delivery to overcome the partial vascular restriction.

Other explanations could be that the partial occlusion with exercise causes oxidative stress markers to peak much later than the 15 min post-exercise time point measured in the Goldfarb study (Goldfarb et al., 2008). The protein carbonyl levels, while not statistically significant, did increase from post-exercise to 15 min post-exercise. Previous investigations have found that protein carbonyls do not always peak immediately following exercise, but instead continued to increase for over an hour post-exercise (Bloomer et al., 2005). One other possibility may be a protective effect from heat shock proteins (HSP) as they are known inhibitors of oxidative stress (Polla et al., 1996) and researchers using a rat model have shown that vascular blood flow restriction increases HSPs (Kawada & Ishii, 2005). This HSP response has been investigated only once with respect to blood

flow restriction exercise in humans, and that study found no increase in HSPs (Fry et al., 2010); however, this study involved an elderly population in which the HSP response is known to be blunted (Hamada et al., 2005; Vasilaki et al., 2006).

In summation, oxidative stress has not been shown to increase in response to low-intensity blood flow restriction training ($\leq 30\%$ 1RM). Despite this, research on this topic is sparse, and much more research is warranted before a definitive opinion can be made on the effects of low-intensity blood flow restriction training on damage from oxidative stress. Research should focus on measuring blood markers of oxidative stress out to at least 24 h post-exercise and ideally up to 48 h. HSPs, known inhibitors of free radicals, should also be measured in younger populations to see what role, if any, they play in the antioxidant defense system.

Muscle damage

Muscle damage occurs during and after unaccustomed exercise, particularly if the exercise involves a large amount of eccentric contractions (Wilson et al., 2009). It is currently thought that the initial muscle damage is proportional to the relative load and thus mechanical perturbations in skeletal muscle, while the inflammatory response that occurs later may explain additional damage following exercise (Clarkson & Hubal, 2002). Because of the inherent errors in assessing whole muscle damage from small biopsy samples, as well as the invasive nature of these techniques, investigators have sought more indirect indices. According to Warren et al. (1999), the three most frequently utilized measures include subjectively estimated soreness from a pain rating scale, strength decrements, and changes in blood protein levels (e.g. creatine kinase and lactate dehydrogenase) (Warren et al., 1999). Our data and others have found that muscle soreness peaks at approximately 24–72 h following exercise (White et al., 2008; Wilson et al., 2009). In general, isokinetic knee extensions result in approximately a marking of 4–5 on a scale of 10 with soreness, while maximal eccentric contractions result in scores as high as 7–8 (Clarkson & Hubal, 2002). However, low-intensity blood flow restriction knee extensor exercise (35% MVC) only resulted in peak soreness scores of 2.8 at 24 h, with no increases in perceived soreness at any other time points (Umbel et al., 2009). In two independent studies, we reported increases in creatine kinase from 140 U/L at rest to values as high as 1100 U/L following leg extension exercise (White et al., 2008; Wilson et al., 2009); however, others have found post-exercise values >5000 U/L using primarily eccentric downhill exercise (Clarkson & Hubal, 2002). In contrast, low-intensity blood flow restriction training has not been shown to result in changes in either creatine kinase or myoglobin content following acute bouts of resistance exercise at 20% 1RM (Takarada et al., 2000a) or walk training at 50 m/min (Abe et al., 2006). While more extensive research needs to be conducted, to this point it appears that low-intensity blood flow restriction training causes only minimal muscle damage.

Nerve conduction velocity

Nakajima et al. (2006) found from their survey of 105 facilities that used blood flow restriction as a training technique that numbness was sometimes reported in response to a blood flow restrictive exercise bout. Although only 1.6% out of 30 000 sessions reported the transient side effect, it raised an important safety question, with respect to the numbness and possible nerve conduction blockage which is often seen following surgery (Lundborg, 1988) or when external compressions are applied to a limb causing both ischemia and a slowing of nerve conduction velocity (NCV) (Denny-Brown & Brenner, 1944; Pedowitz et al., 1991; Mittal et al., 2008).

Clark et al. (2010) investigated the overall integrity of sensory motor nerve conduction by estimating NCV from the latency responses in H-reflex recordings. NCV was unchanged after 4 weeks of low-intensity blood flow restriction training (30% 1RM). This was an expected outcome because the overall length of the restrictive exercise bout only lasted approximately 10–15 min. Surgery, which requires much longer durations of occlusion, is associated with a transient slowing in NCV, which is rapidly reversed and rarely results in permanent nerve damage (Lundborg, 1988).

In summation, low-intensity blood flow restriction training (30% 1RM) does not seem to have a chronic negative effect on NCV in healthy human subjects. Future research should investigate the NCV effects of an acute blood flow restriction training bout to see if any short-term impairment occurs, and if so, the time course of that impairment. In addition, focus should be placed on long-term studies greater than 4 weeks, to determine what effect longer term training has on H-reflex amplitudes during blood flow restriction exercise because increases have been noted following chronic resistance training (Aagaard et al., 2002; Lagerquist et al., 2006; Holtermann et al., 2007).

Pressure recommendations for future research

Following a careful review of the literature, numerous pressures have been used for restricting blood flow. These restrictive pressures generally range from

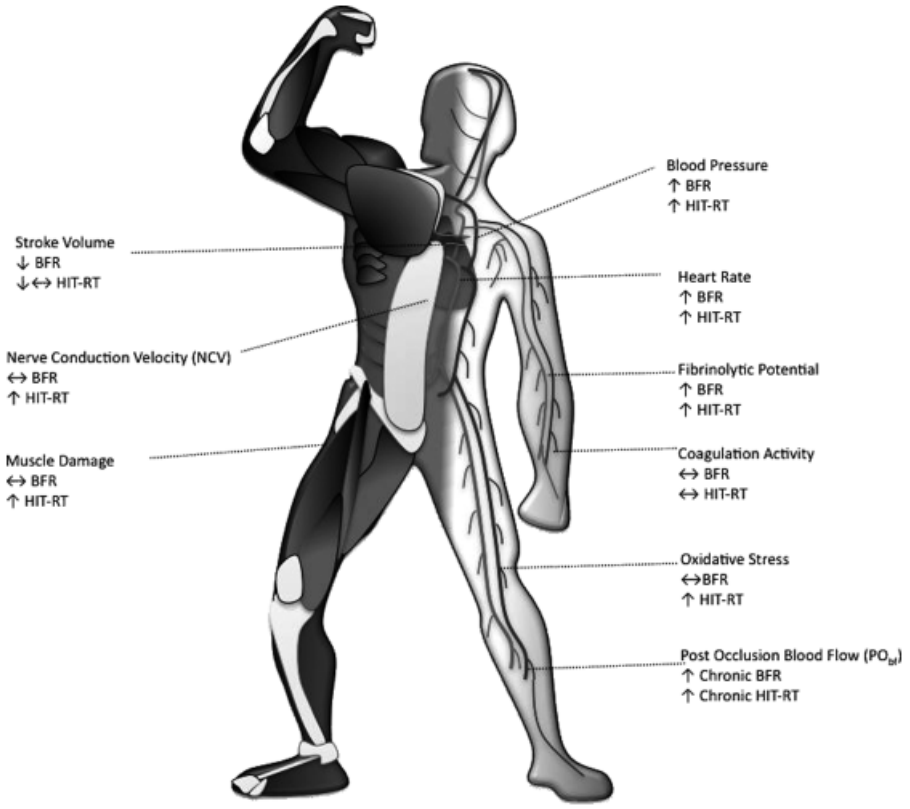

Fig. 1. Summary of the potential safety issues with blood flow restriction (BFR) compared with high-intensity resistance training (HIT-RT). Responses for each were as follows: ↑, increases; ↓, decreases; ↔ , no change.

approximately 1.3 times greater than systolic blood pressure (~ 160 mmHg) to upwards of 200 mmHg. In most published reports, the width of the belt used to restrict blood flow is often times ignored. However, the width of the restrictive device is of importance because wider cuffs transmit pressure differently than narrow cuffs (Crenshaw et al., 1988), thus applying 200 mmHg across 50 mm with a KAATSU Master cuff which will likely produce a different stimulus than 200 mmHg applied over 135 mm with a different cuff. Crenshaw et al. (1988) demonstrated that wider cuffs restrict blood flow at a lower overall pressure than a narrow belt. Additionally, Shaw and Murray (1982) observed that limb circumference is also a determining factor in the level of blood flow restriction from a given pressure, especially with a narrow cuff. They demonstrated using an 80 mm wide cuff, a consistent decrease in the mean maximal tissue-fluid pressure as the circumference of the limb increased. However, although a wider cuff may produce a greater level of restriction with lower pressures, Mittal et al. (2008) has shown that a wider cuff also produces a greater reduction in NCV when compared with a narrow cuff (140 vs 70 mm).

In summary, perhaps the pressures used to restrict blood flow should to some degree be determined by the width of the cuffs and limb circumference, and not necessarily by pressures previously used in the literature. Investigators should also consider the possible NCV impairments that may occur from using a wider cuff (Mittal et al., 2008).

Perspectives

This review focused on what is currently known about the safety of blood flow restriction training and how this compares to exercise under normal blood flow conditions (Fig. 1). The research, while positive, is limited and more research should be completed to better determine under what conditions this type of training can be safely used. In addition, the width of the belt and limb circumference should be accounted for when applying the restrictive stimulus to each subject. In conclusion, the current research on blood flow restriction training with respect to safety outcomes confirms earlier reports that blood flow restriction exercise, when used in a controlled environment by trained and experienced personnel, provides a safe training alternative for most individuals regardless of age and training status.

Key words: KAATSU, cardiovascular, muscle damage, hypertrophy.

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