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Twenty-five years of blood flow restriction training: What we know, what we don't, and where to next?

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ABSTRACT

Blood flow restriction is a technique that involves inflating a cuff at the proximal portion of the limb with the goal of reducing arterial inflow into the muscle and venous outflow from the muscle. Low-load or low-intensity exercise in combination with blood flow restriction has been consistently shown to augment adaptations over the same/similar exercise without restriction, with changes in muscle size and strength being two of the most commonly measured adaptations. The purpose of this manuscript is to provide an updated narrative review on blood flow restriction. Blood flow restriction's history, methodology, safety, and efficacy are highlighted. We discuss the effects of blood flow restriction on changes in muscle size and strength, and also review work completed on other variables (e.g. bone, resting blood flow, tendon, pain sensitivity, cognition, orthostatic intolerance). We finish by highlighting six possible areas for future research: 1) identifying mechanisms for growth and strength; 2) sex differences in the effects of blood flow restriction; 3) individual responses to blood flow restriction; 4) influence of pressure versus amount of blood flow restricted; 5) application of blood flow restriction with higher-loads; and 6) what considerations should be made to test the effects of blood flow restriction.

KEYWORDS

Occlusion training; kaatsu; practical blood flow restriction; muscle adaptation; exercise

Introduction

Blood flow restriction is a technique that involves inflating a cuff at the proximal portion of the limb with the goal of reducing arterial inflow into the muscle and venous outflow from the muscle (Mattocks et al., 2018; Patterson et al., 2019). Low-load or low-intensity exercise in combination with blood flow restriction has been consistently shown to augment adaptations over the same/similar exercise without blood flow restriction (Loenneke, Wilson, et al., 2012; Scott et al., 2016); with changes in skeletal muscle size and strength being two of the most commonly measured adaptations (Lixandrao et al., 2018). These effects have even been observed at muscles proximal to the cuff (Dankel, Jessee, et al., 2016; Pavlou et al., 2023). The popularity of this technique appears to be increasing in and out of the laboratory (Patterson & Brandner, 2018), however, it is important to note that this technique has been around for more than 20 years (Burgomaster et al., 2003; Shinohara et al., 1998; Takarada, Takazawa, et al., 2000). Yoshiaki Sato is often credited as the inventor of this technique with legend (i.e. veracity of which is not known) saying that this idea was revealed to him while kneeling at a Buddhist ceremony (Sato, 2005). The blood circulation was reduced, and he likened this to how he felt after a bout of heavy exercise. This led Sato to experiment with a variety of methods before finally releasing his method 'KAATSU' (the addition of pressure in Japanese) to the general public (Sato, 2005). While this origin story is potentially apocryphal, it is clear that Yoshiaki Sato is an important reason why blood flow restriction is as well studied as it is.

Shinohara et al. (1998) published the first paper on this technique in 1998. Those authors found that short-term training with blood flow restriction was able to increase strength over the opposite limb training without blood flow restriction. To be clear, there are numerous papers that have inflated cuffs on limbs during exercise before this paper (Alam & Smirk, 1937; Duncan et al., 1981; Signorile et al., 1991; Stanley et al., 1985). However, to our knowledge, Shinohara et al. (1998) was the first study applying the cuff with the goal of partially restricting blood flow in order to see beneficial adaptations to skeletal muscle. Following that study, numerous laboratories have investigated the effects of blood flow restriction with and without exercise (Patterson et al., 2019). Over the past 25 years, a wealth of knowledge has been gained about blood flow restriction. However, much still remains unknown. The purpose of this manuscript is to provide an updated narrative review of the blood flow restriction technique. The goal of this paper is not to be an exhaustive review of each selected topic but to provide an overview on what is known, unknown, and some possible avenues for future research in the realm of blood flow restriction.

Method of application for blood flow restriction

Early on in the blood flow restriction literature, cuffs were applied and inflated to the same pressure for everyone (Shinohara et al., 1998; Takarada, Takazawa, et al., 2000). This

was often discussed in the literature as ‘arbitrary’ but simply meant that the applied pressure did not account for the individual characteristics to which the cuff was being applied (Loenneke, Fahs, et al., 2013). Current recommendations suggest that the pressure applied should account for the specific cuff being used and the individual to which the cuff is being applied (Patterson et al., 2019). Cuff width has a major impact on the applied pressure (Jessee et al., 2016; Loenneke, Fahs, Rossow, Abe, et al., 2012), with a wider cuff requiring lower pressures than a narrower cuff (e.g. 12 cm wide vs. 5 cm wide). In addition, larger limb circumferences tend to require greater pressures than smaller limb circumferences (Loenneke, Allen, et al., 2015; Loenneke, Fahs, Thiebaud, et al., 2012). In theory, both of these variables can be accounted for by taking what is known as the arterial occlusion pressure; defined as the lowest pressure applied at which there is no blood flow into the limb. This is a relatively simple measurement (similar to blood pressure), which involves placing a cuff at the top of the limb and applying something that can detect a pulse at an artery distal to the cuff (e.g. hand-held Doppler probe). The cuff is inflated, and the pressure is slowly increased until the pulse disappears. The pressure at which the pulse disappeared would serve as the arterial occlusion pressure. The cuff would then be inflated at a percentage of that value (e.g. 40% resting arterial occlusion pressure). Of note, applying a percentage of resting arterial occlusion pressure does not necessarily result in equivalent reductions in blood flow. In other words, 40% arterial occlusion pressure does not mean that arterial blood flow is reduced by 40% (Mouser et al., 2018).

Other variables such as biological sex (Jessee et al., 2016), cuff chamber number (Rolnick et al., 2023), cuff material (Buckner et al., 2017; Loenneke, Thiebaud, et al., 2013) and posture (Hughes et al., 2018; Karanasios et al., 2022) may also impact the pressure needed to achieve arterial occlusion. Limb dominance (Tafuna’i et al., 2021) may also impact the arterial occlusion pressure, but any effect is expected to be small and indistinguishable from error in most individuals (Yamada, Hammert, Kataoka, Song, Kang, & Loenneke, 2025). Regardless, all of these factors would theoretically be accounted for by taking the arterial occlusion pressure. There are, however, some caveats. Arterial occlusion pressure cannot always be achieved for every individual (due to limits of the equipment used). Previous work has found that cuffs that are 12 cm in width are able to cut off the majority (if not all) participants but 5-cm-wide cuffs cannot (Yamada, Kang, et al., 2023); particularly in the lower body where the limbs are bigger. We have found a detectable pulse in some participants with pressures as high as 900 mmHg, which is almost certainly related to how the cuff bladder in a narrower cuff interacts with the limb (Spitz, Yamada, et al., 2024). The chamber number may also impact the ability to detect arterial occlusion. As noted by Rolnick (2024), traditional cuffs are single-chambered, which results in largely equal circumferential pressure around the limb. However, multi-chambered cuffs make achieving arterial occlusion pressure difficult due to the gaps between the sequential bladders. Ultimately, the decision to use one cuff

versus the next may come down to feasibility (i.e. which cuff does the researcher have access to) and/or personal preference. Our laboratory has traditionally favored narrower cuffs due to the potential for attenuated growth directly under the cuff (Ellefsen et al., 2015; Jakobsgaard et al., 2018; Kacin & Strazar, 2011) and the augmented perceived discomfort (particularly in the upper body) when using wider cuffs with exercise (Spitz et al., 2019). However, given the aforementioned limitations of not being able to measure arterial occlusion (Yamada, Kang, et al., 2023), practitioners may prefer to use a wider cuff in the lower body to ensure that a relative pressure can be applied.

One final consideration is the cuff system/device itself (Hughes et al., 2025). Some devices are able to auto-regulate the pressure during the exercise whereas others cannot. Autoregulated pressure means that air is pumped into and out of the cuff based on changes in pressure from muscle relaxation and contraction. Work has found some differences in acute exercise between auto-regulated and non-regulated devices. These differences were observed even though the cuff was inflated to the same percentage of resting arterial occlusion pressure (Jacobs et al., 2023; Rolnick et al., 2024). Gaining a greater understanding of the nuances of a blood flow restriction device is an important area of research; however, we must ensure that we do not miss the forest for the trees. Long-term physiological improvement or recovery post injury is a large reason why blood flow restriction is applied. Two systems may produce small acute differences, but those differences may not lead to differential physiological changes across time. This is not to discount differences in the acute response to blood flow restricted exercise, as that can certainly impact the feasibility of using blood flow restriction long enough to see beneficial adaptations. Whatever system ends up being used, authors should clearly specify the device as well as the cuff (Hughes et al., 2025). This will help researchers to better assess the long-term implications of using a particular blood flow restriction system and also allow practitioners to make better informed decisions.

What about practical blood flow restriction?

Blood flow restriction is typically set relative to a known pressure within the laboratory and clinic. However, this limits the use of blood flow restriction for the typical gym-goer who may be unable to pay for the more expensive devices. Practical blood flow restriction was first introduced into the literature by Loenneke and Pujol in 2009 and refers to situations where a knee wrap or cuff is applied to the limb of interest without quantifying the pressure (Loenneke & Pujol, 2009). Follow-up work recommended applying the wrap at a ‘7’ out of 10 on a perceived tightness scale (Wilson et al., 2013) but subsequent work has found that approach to be unreliable and one that produces a wide range of relative pressures (Bell et al., 2018; Bell, Dankel, et al., 2020). Other methods of application include teaching the participant to sense the correct pressure (Bell et al., 2022; Bell, Spitz, et al., 2020; Bjornsen et al., 2019) and applying the cuff/wrap to a percentage of the resting limb circumference (Abe et al., 2019). Notwithstanding the limitations of practical blood flow restriction, there is work suggesting that this method may be able improve both muscle size and

strength (Lowery et al., 2014; Luebbbers et al., 2014; Yamanaka et al., 2012).

Is blood flow restriction safe?

The question with safety is not whether there is risk associated with blood flow restriction but whether the risk is greater than that observed with the same exercise without blood flow restriction and how it compares to that of more traditional higher load/intensity exercise. It is important to remember that the goal of applying blood flow restriction is to partially reduce blood flow into the limb and that this partial restriction is only applied for minutes not hours (Patterson et al., 2019).

Blood clotting and muscle damage are two commonly expressed concerns with blood flow restriction. However, both of these concerns appear to be largely unfounded based on the available literature (Loenneke et al., 2011). The application of blood flow restriction does not appear to negatively affect the balance between coagulation and fibrinolytic activity (Clark et al., 2011; Madarama et al., 2010). Further, although muscle fibers are stressed with blood flow restricted exercise (Cumming et al., 2014; Nielsen et al., 2017), there does not appear to be structural damage. Although there is some degree of soreness (Sieljacks et al., 2016; Umbel et al., 2009) associated with this exercise (particularly early on) that in and of itself is not a surrogate of muscle damage. The soreness, which is also observed following traditional resistance training, diminishes with time due to the repeated bout effect (Sieljacks et al., 2016).

Blood pressure acutely increases in response to low-load resistance exercise (Downs et al., 2014; Hammert, Song, et al., 2024; Yamada, Hammert, Kataoka, Song, Kang, & Loenneke, 2025). A large part of this increase is likely related to the build-up of metabolites associated with blood flow restricted exercise (Yamada, Hammert, Kataoka, Song, Kang, Kassiano, et al., 2025). The change in blood pressure is often greater than that of the same exercise without blood flow restriction (Brandner et al., 2015; Downs et al., 2014; Hammert, Song, et al., 2024), but the magnitude of this change is within physiological norms of exercise. However, concerns have been raised that there could be some individuals who are more sensitive to metabolites which could cause them to have an exaggerated blood pressure response to this type of exercise (Spranger et al., 2015). Although that is a real possibility, proper application of blood flow restriction and monitoring those who are naïve to this exercise could largely mitigate this risk. Moreover, blood pressure has been shown to return back towards baseline levels by 5–10-min post-exercise (Rossow et al., 2012). Whether repeated bouts of blood flow restricted exercise impacts resting levels of blood pressure is surprisingly not well studied. A previous meta-analysis only had a few studies that met the inclusion criteria so that will be an important area of future research (Wong, Song, et al., 2022). Notably, a recent paper with a relatively large sample size did not see a change in resting blood pressure following repeated bouts of blood flow restricted exercise (Spitz, Wong, et al., 2024).

The final point on safety is that the majority of studies have been relatively small in scale. Although this stimulus has been applied safely to a variety of populations (e.g. children, adults, older adults, injured, those with myopathies, etc.), it is unlikely

that we have a full safety profile of the blood flow restriction stimulus. Even studies with larger sample sizes will often miss rare events because by definition they are uncommon (Onakpoya, 2018). Case studies on blood flow restriction will be helpful and informative as this stimulus is applied moving forward so that we are able to better figure out who blood flow restriction works best for and who may want to forego the use of this stimulus. Reporting whether there were harms or adverse events during a research study will also improve our understanding of the risk involved with blood flow restriction (Bandholm et al., 2022). Many researchers (including us) traditionally only state adverse events if they happen, but it is as equally important to document when there are no observed harms or adverse events within a research study.

An overview of how blood flow restriction has been implemented

Blood flow restriction by itself

The application of blood flow restriction in the absence of muscle contraction is similar to ischemic preconditioning in that there are periods of ischemia followed by periods of reperfusion. Some researchers may view them as being synonymous (Patterson et al., 2019). In the realm of blood flow restriction, Takarada et al. (2000) presented the first evidence that inflating and deflating a cuff to a limb, even in the absence of muscle contraction, could attenuate atrophy of the quadriceps following anterior cruciate ligament surgery. This was followed up by additional work which found that a series of inflations and deflations helped attenuate the loss of muscular strength during different forms of immobilization (Takehi et al., 2020; Kubota et al., 2008, 2011). There were suggestions in the literature that these beneficial effects might be related to the acute muscle cell swelling that is observed with blood flow restriction (Loenneke, Fahs, Rossow, Abe, et al., 2012, 2012). It was hypothesized that blood flow restriction induced cell swelling which would then subsequently turn on anabolic signaling (Loenneke, Fahs, Rossow, Abe, et al., 2012). However, recent work has found that blood flow restriction by itself (in the absence of contraction) did not favorably impact myofibrillar protein synthesis (Nyakayiru et al., 2019). If there is benefit of cell swelling, then this might mean that any favorable effect could be working through changes in protein breakdown (e.g. suppression of MURF1) (Takehi et al., 2020). Alternatively, given that the aforementioned study (Nyakayiru et al., 2019) was conducted in healthy young men under resting conditions, it may be that the benefits are only observed when a limb has been immobilized.

Although early studies showed promise, two recent studies have failed to find a blood flow restriction-induced attenuation in atrophy or strength with immobilization from bed rest (Fuchs et al., 2024) or from a knee brace (Slysz et al., 2021). Collectively, it appears that the application of blood flow restriction by itself may not always be enough of a stimulus to slow down muscle loss. However, it should be noted that the literature is mixed with respect to the designs used to investigate the effects of blood flow restriction on muscle disuse atrophy. Although the atrophy process likely varies based on the modality of disuse, it

nonetheless seems likely that some form of muscle contraction is important for maintaining skeletal muscle tissue (S. B. Cook et al., 2010). This contraction does not have to be voluntary, as benefits have been observed with electrical stimulation in combination with blood flow restriction (Natsume et al., 2015; Slys et al., 2021). It is noted that a previous paper did not find a slowing of muscle atrophy even with contractions (Iversen et al., 2016); however, the apparent difference in time from injury to surgery between groups was a limitation of that particular study.

Aerobic exercise + blood flow restriction

There are some data suggesting that aerobic-type exercise with blood flow restriction can produce favorable changes in muscle size, strength, physical function, and aerobic capacity (Bennett & Slattery, 2019; Clarkson et al., 2017; de Lemos Muller et al., 2024). Studies have used this mode of blood flow restriction by inflating cuffs at the top of the leg during slow walking or low-intensity cycling. Early work from Abe et al. (2006) found that when young adults walked slowly with blood flow restriction, they were able to increase muscle size and strength to a greater extent than the same exercise without blood flow restriction. Other work has found similar support for low-intensity cycling (Abe et al., 2010; Conceicao et al., 2019). In addition, aerobic capacity may also improve through the use of blood flow restriction (Bennett & Slattery, 2019; Thompson et al., 2024), but conclusions are tempered due to the large differences in methodology between the available studies (i.e. pressure applied, exercise intensity, comparator groups, etc.). We suspect that the likelihood of observing beneficial muscle adaptations with low-intensity aerobic exercise in combination with blood flow restriction may increase in those who are older or for those who may not yet be able to complete resistance-type exercise due to some injury.

Given that athletes (who require high power outputs for their sport) may not want to spend time training with lower intensities (i.e. training slowly), there has been increased interest in using blood flow restriction during higher intensity aerobic exercise (e.g. running and cycling). Some work in athletes has found improvements in markers of performance following running with blood flow restriction (Behringer et al., 2017; Chen, Hsieh, Ho, Ho, et al., 2022, 2022); however, the majority of work has investigated the effects of combining blood flow restriction with higher-intensity cycling (Mitchell et al., 2019; Pugh et al., 2024; Taylor et al., 2016). In those studies, the restriction has been applied almost exclusively during the rest periods (Taylor et al., 2016). This ensures that the contractions during the sprints are not impaired by the application of blood flow restriction (McKee et al., 2024); however, it may also allow the limb to receive benefits from the repeated bouts of restriction and reperfusion. This strategy has been found to improve aerobic capacity in trained individuals but that improvement did not translate to an enhanced time-trial performance (Taylor et al., 2016). Although the aforementioned work has inflated the cuff during the rest period, there is also work suggesting a benefit when the cuff was inflated during the contraction itself (Christiansen et al., 2019; Tangchaisuriya et al., 2022). To illustrate, a paper published in Master level cyclists found that implementing blood flow

restriction into a high-intensity interval program (during some of the contractions) improved muscle size, muscle strength, and peak power over groups not including blood flow restriction (Tangchaisuriya et al., 2022). Ferguson et al. (2021) have presented intriguing ideas on strategies for using blood flow restriction to enhance muscle adaptation and performance in endurance-trained athletes, and it will be interesting to see how this technique is utilized in the future.

Resistance exercise + blood flow restriction

The majority of the literature with resistance exercise has focused on low-loads (20–30% of maximum strength) in combination with blood flow restriction (Patterson et al., 2019). Relatively less work has been completed with blood flow restriction and higher-loads (discussed in future directions). Numerous independent laboratories have found that low-load resistance exercise in combination with blood flow restriction is able to increase muscle size comparable to that of traditional high-load training (Lixandrao et al., 2018). This increase in muscle size at the whole muscle level appears to be due to increases in both Type 1 and Type 2 fiber size (Libardi et al., 2024; Wang et al., 2023). Maximal strength (in the task trained) also improves when blood flow restriction is applied, however, the strength gained is typically less than that observed with traditional high-load resistance exercise (S. B. Cook et al., 2017; Lixandrao et al., 2018; Martin-Hernandez et al., 2013; Wong, Spitz, Song, et al., 2024). These improvements in strength have even been observed in those recovering from knee injuries (S. Li et al., 2021). In fact, strength gain from blood flow restricted exercise was comparable to that of higher load exercise in patients recovering from anterior cruciate ligament reconstruction (Hughes et al., 2019) and in those receiving treatment for patellofemoral pain (Giles et al., 2017).

Over the past decade, research has suggested that blood flow restriction is less likely to result in augmented size and strength if the low-load exercise is taken to or near failure (Fahs et al., 2015; Farup et al., 2015; Jessee et al., 2018; Pignanelli et al., 2020). When the effects of low-load training to failure with and without blood flow restriction are compared, changes in muscle size and strength were shown to change similarly; however, the blood flow restriction group has to complete less volume of work for a similar effect (Fahs et al., 2015; Farup et al., 2015; Pignanelli et al., 2020). This is not to say that going to failure equalizes everything though. For example, changes in local muscular endurance (Jessee et al., 2018) and the cross-education of strength (Wong, Spitz, Song, et al., 2024) can be augmented by the application of blood flow restriction even when the comparator groups are training to or near failure. It is clear that muscular failure is not required for the beneficial effects from blood flow restricted exercise (Sieljacks et al., 2019); however, it is not yet known how submaximal the exercise can be and still elicit adaptations (discussed more in future directions).

Outcomes other than muscle size and strength

Muscle size and strength are two of the most commonly studied outcomes within the blood flow restriction literature, likely

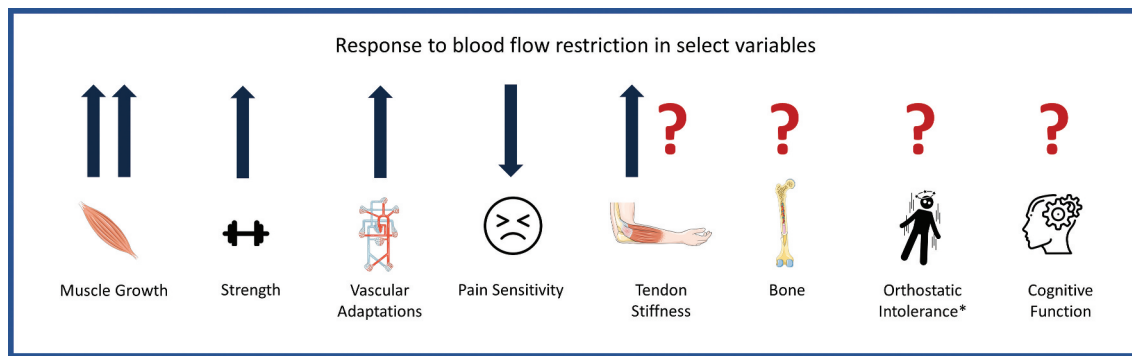


Figure 1. Response to blood flow restriction in select variables. Arrows indicate directional change. We elected to put two arrows for muscle growth given how pronounced the effect is in most studies. Tendon stiffness also includes a question mark because it has been compared to high-load exercise but not low-load exercise without blood flow restriction. Orthostatic intolerance has an * to indicate that this has been studied in the absence of exercise.

because both of those variables are associated with beneficial health outcomes (R. Li et al., 2018; Wolfe, 2006) and athletic performance (Suchomel et al., 2016; Ye et al., 2013). Notably, there has also been research on bone, resting blood flow, tendons, pain sensitivity, cognition, and even some work on using blood flow restriction to combat orthostatic intolerance (to name a few). Each of these will be briefly discussed, but it is clear that these variables require additional work to determine if, when, and for whom these variables can be favorably altered by blood flow restriction (Figure 1). We acknowledge that there are other variables that have also been investigated and could have been discussed. However, we elected to discuss the aforementioned variables because we thought they have received relatively less attention in the literature and provide the greatest opportunities for future research.

Bone

Bone is a dynamic tissue that can remodel following periods of loading (Willems et al., 2017). Because load is considered an important stimulus for the osteogenic response (Turner, 1998), traditional higher-load resistance training is often recommended over lower-load resistance training (Brooke-Wavell et al., 2022; Kohrt et al., 2004). However, little work has been done to determine whether blood flow restriction may be able to augment the osteogenic signal of lower-load exercise (Bittar et al., 2018). It was hypothesized that the fluid pressure with lower oxygen tension observed with blood flow restriction might provide a stimulus for favorable bone remodeling (Loenneke, Young, et al., 2012). In fact, a case report provided suggestive evidence for bone healing in a patient with an osteochondral fracture (Loenneke, Young, et al., 2013). The application of blood flow restriction may also help maintain bone mass after anterior cruciate ligament reconstruction (Jack et al., 2023). However, the evidence for improving bone health via blood flow restriction is limited, which may be related to the longer durations of time required to observe changes in bone. Bone markers in the blood indicate that lower load exercise in combination with blood flow restriction may be able to produce beneficial changes in bone (Karabulut et al., 2011). However, more research that measures actual changes in bone is necessary in order to know whether blood flow restriction can have a favorable impact.

Resting limb blood flow

Lower load exercise with blood flow restriction has been shown to augment vascular adaptations over the same exercise without blood flow restriction (Hunt et al., 2013; Patterson & Ferguson, 2010, 2011). Studies have found increased gene transcription associated with angiogenesis (Ferguson et al., 2018; Larkin et al., 2012), and data at the fiber level indicate that capillaries may be increasing in number (Nielsen et al., 2020). Measurements of resting limb blood flow indicate that higher pressures may be needed in order to stimulate changes in the vasculature to levels observed with traditional higher load exercise (Mouser et al., 2019). The improvements in the vasculature may increase nutrient delivery to the muscle and may play some role with the muscle growth that is observed with blood flow restricted exercise. Future work is needed in order to better determine how pressure impacts these long-term changes in resting limb blood flow and whether the effect of pressure depends upon the exercise load used. Our suggestion that vascular changes are pressure dependent (Mouser et al., 2019) also requires further study and independent confirmation. Lastly, whether baseline limb blood flow or the change in that variable impacts muscle growth could be addressed through moderation (Hayes & Rockwood, 2017; Montoya, 2019) and mediation analysis (Hayes & Rockwood, 2017; Montoya & Hayes, 2017). A recent paper on young healthy adults implemented this method but did not find a role of resting limb blood flow for changes in muscle size (Wong, Spitz, Bentley, et al., 2024). Whether this finding is consistent with other exercise interventions or populations requires further study.

Tendon

The initial work investigating the impact of blood flow restriction on tendon was conducted by Kubo and colleagues in 2006 (Kubo et al., 2006). The authors hypothesized that the lactate pooled in the working muscle might serve as a stimulus for collagen production by resident tissue macrophages. However, they did not find pre-post improvements in tendon stiffness or cross-sectional area with blood flow restricted exercise, but tendon stiffness did increase for the high-load condition. This indicated that the load might have been too low in the blood

flow restriction condition to see improvements in the tendon. The lack of progression in exercise load across 12 weeks in the limb exercising with blood flow restriction is an important caveat to that study. In addition, the use of an absolute pressure in that study may also be worth considering. More recent work, which has progressed the load, and applied relative pressures (50% of the resting arterial occlusion pressure) has found improvements in tendon stiffness (Centner et al., 2019, 2022) and cross-sectional area (Centner et al., 2019, 2022, 2023). These changes have exceeded a non-exercise control (Centner et al., 2019) and were similar to that observed with traditional high-load training (Centner et al., 2019, 2022, 2023). However, it is not known what effect low-load exercise would have had without blood flow restriction, because that protocol was not included. This makes it difficult to know what role blood flow restriction had on these findings (i.e. whether blood flow restriction is actually an effective stimulus for changing tendon). Future work is needed to determine the impact of blood flow restriction on tendinous adaptations. Studies could also investigate the interaction between pressure and load to determine the potential interplay between those variables on changes at the tendon.

Pain sensitivity

Exercise with blood flow restriction reduces pain sensitivity (as measured by pressure pain threshold) acutely over exercise without blood flow restriction (Hammert, Song, et al., 2024; Hughes & Patterson, 2020; Hughes et al., 2021). This effect is systemic, occurring in exercised and unexercised limbs. This reduction in pain has been linked to the discomfort (i.e. pain inhibits pain) and the endogenous opioid production observed with this form of exercise (Hughes & Patterson, 2019; Song et al., 2021). Although our own laboratory has repeatedly found reductions in pain sensitivity with exercise in combination with blood flow restriction (Hammert, Song, et al., 2024; Song et al., 2023; Song, Yamada, Wong, et al., 2022), we have not been able to find a mediating role for discomfort (Hammert, Song, et al., 2024; Song et al., 2023). This reduction in pain sensitivity has been observed in response to a mechanical stimulus (e.g. algometer pressed to tissue) but has not yet been observed with other noxious stimuli such as ischemia (Hammert, Song, et al., 2024). The utility of this reduction in pain sensitivity is not entirely clear, but some have hypothesized that blood flow restriction could be applied prior to therapy (Korakakis et al., 2018) so that a higher-quality therapy session might be achieved (e.g. use a greater load, achieve a greater range of motion). There is also evidence that blood flow restriction itself (in the form of ischemic preconditioning) can reduce pain sensitivity (Kataoka et al., 2024); although this reduction in pain was not linked with improved exercise performance. Whether this reduction in pain is something that is beneficial requires additional work and clinical scrutiny. It might be speculated that part of the functional improvement observed in clinical populations might be related to this analgesic effect of blood flow restriction (Giles et al., 2017). Research on other variables of pain also requires further study. For example, pain tolerance has been less studied, but preliminary data were not able to find a benefit of blood flow

restriction (Hammert, Song, et al., 2024). More work is necessary, but blood flow restriction appears to induce systemic reductions in pain sensitivity for an unknown duration of time (i.e. at least 5 min and maybe as long as 24 h). This will be an important area of future research, particularly as it relates to clinical settings. A final consideration is whether blood flow restriction can chronically alter pain sensitivity (i.e. training-induced hypoalgesia) (Song, Yamada, Kataoka, et al., 2022) which would also have important clinical ramifications.

Cognitive function

Traditional exercise has been shown to improve (acute effect) multiple domains of cognition (Chang et al., 2012; Wilke et al., 2019). Executive function is one domain that is particularly well studied and has been shown to improve acutely following an exercise bout (Pontifex et al., 2019). This improvement is often observed with aerobic-type exercise, and some have hypothesized that this improvement in cognitive function is fueled, in part, by the lactate produced from the working muscle (Brooks et al., 2022; Hashimoto et al., 2018). Walking with blood flow restriction has been shown to improve interference control (Sugimoto et al., 2021). However, the work completed with resistance-like exercise in combination with blood flow restriction has not been able to show improvements over the same exercise without blood flow restriction (Sardeli et al., 2018; Yamada Song et al., 2021). Future work is needed to compare pressures, intensities, and types of exercise (Yamada, Frith, et al., 2021). For example, our laboratory has shown that sprint interval training with blood flow restriction and cooling can improve interference control over a non-exercise control (Yamada, Kataoka, et al., 2023); however, it is not known how this would compare with lower-intensity exercise in combination with blood flow restriction. In addition, although lactate is hypothesized to be a mechanism for the observed improvement, we were not able to find evidence of lactate being a mediator for that improvement (Yamada, Kataoka, et al., 2023). Future work could seek to investigate other domains of cognitive function in order to see which domain is most likely to be favorably impacted by blood flow restriction. The chronic changes in cognitive function following blood flow restricted exercise would also be an interesting area to explore (Torpel et al., 2018).

Orthostatic intolerance

Postural shifts are associated with immediate changes within the cardiovascular system. Finding ways to induce these cardiovascular effects may have benefits to individuals preparing to return from space (Hackney et al., 2012; Jordan et al., 2022; Loenneke & Pujol, 2010). Early work suggested that the application of blood flow restriction in the supine position could produce a response similar to that observed within the standing position (Iida et al., 2007). Stroke volume reduced and heart rate and total peripheral resistance increased in response to the restriction of blood flow. Those authors recognized that this might serve as an important countermeasure to orthostatic intolerance following spaceflight. Our laboratory investigated the influence of different levels of blood flow restriction on the blood pressure response during

a head-up tilt-test (Wong, Bell et al., 2022). We found that the application of blood flow restriction prevented the immediate decrease in blood pressure with head-up tilt. That study was a proof of concept study but opened up the possibility for use in those returning from space who may be suffering from orthostatic intolerance; particularly if there is an emergency and the capsule needs to be evacuated quickly. The inflation of cuffs to the limbs could help maintain pressure during the emergency exit, allowing the individual to safely escape (Wong, Bell et al., 2022). This might be even more important with the emergence of civilian space travel (Stepanek et al., 2019). However, our findings need to be verified in those who have documented orthostatic intolerance. The possible utility of blood flow restriction to help maintain blood pressure during postural shift could also be of real clinical utility (provided it is efficacious). The use of blood flow restriction for combatting orthostatic intolerance requires much more work.

Possible future directions

Admittedly, there is still much to learn about blood flow restriction. The supply of research questions in blood flow restriction is inexhaustible (e.g. methodological factors, new or underexplored physiological outcomes, etc.) but we will pay direct attention to six possible directions for future research in this field (Figure 2).

What explains the exercise-induced increase in muscle size and strength?

Low-intensity aerobic exercise in combination with blood flow restriction can induce skeletal muscle growth in some populations (de Lemos Muller et al., 2024). In addition, low-load resistance exercise in combination with blood flow restriction induces large changes in muscle size similar to that of traditional high-load exercise (Kim et al., 2017; Takarada, Takazawa, et al., 2000). Although the growth with blood flow-restricted resistance exercise is similar to high-loads, a common question is whether the mechanisms are different. Our group originally thought so based on early work that found muscle growth from using blood flow restriction with loads (e.g. $\leq 30\%$ 1RM) which were traditionally believed to be incapable of stimulating changes in healthy populations. Some of that work suggested the large acute hormonal response as a potential mechanism for skeletal muscle growth. For example, Takarada et al. found that blood flow restricted exercise acutely increased growth hormone ~ 290 times over resting levels (Takarada, Nakamura, et al., 2000). However, recent work with (G. C. Laurentino et al., 2022; Ozaki et al., 2017) and without (Morton et al., 2016; West et al., 2010) blood flow restriction indicates that the acute hormonal response to exercise is unlikely to be an important signal for muscle growth, suggesting that these changes are driven by local changes at the exercising muscle. With that in

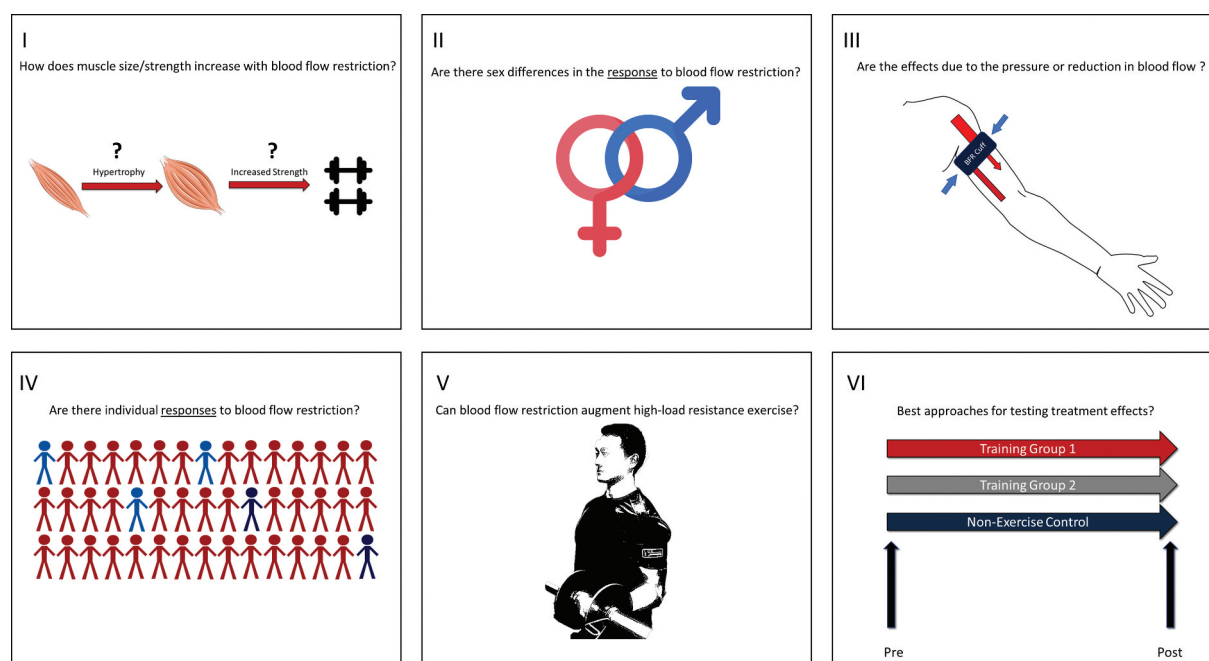


Figure 2. Six possible future directions for blood flow restriction research. (I) What explains the blood flow restriction induced increase in muscle size and strength? Are there unique mechanisms for muscle growth and what role does that growth play with the increased strength? (II) are there sex differences in the response to blood flow restriction? In other words, does the response to blood flow restricted exercise depend upon biological sex? (III) are the effects of blood flow restriction due to the pressure applied or from the reduction in blood flow from the applied pressure? This is a difficult but important question to answer in order to better understand the effects of blood flow restriction. (IV) are there individual responses to blood flow restriction? Does everyone receive a similar benefit or are there some who may respond more favorably to blood flow restricted exercise? (V) can blood flow restriction augment high-load resistance exercise? There may be unique ways of applying pressure that do not negatively impact high-load resistance exercise performance which may then lead to improvements in some outcomes. (VI) what is the ideal approach for testing treatment effects with blood flow restriction? How can we ensure that groups can be randomly assigned while also being matched so that the only difference between groups is the application of blood flow restriction?

mind, the acute and chronic changes in gene expression are similar between low-load exercise with blood flow restriction and high-load exercise (Davids et al., 2021; Ellefsen et al., 2015). Further, there are changes in muscle protein synthesis (Fry et al., 2010; Fujita et al., 2007), and these early changes are blunted through rapamycin (Gundermann et al., 2014). Other studies have found that satellite cells proliferate (Nielsen et al., 2012), myostatin is decreased (G. C. Laurentino et al., 2012), and E-3 ligases are downregulated (Manini et al., 2011) following blood flow restricted exercise/training. These are all changes that would be expected to occur with traditional high-load resistance exercise (Marcotte et al., 2015). The similarities between high-load and low-load resistance exercise with blood flow restriction support the idea that the amount of muscle growth is ultimately related to a large amount of muscle being activated for a sufficient duration of time (Marcotte et al., 2015). Blood flow restriction applied continuously (i.e. throughout exercise and rest periods) traps metabolites around the working muscle, making the muscle work harder than it otherwise would (Suga et al., 2012). In order to maintain the exercise, more and more muscle is activated. By the end of the exercise, a large portion of the muscle has been activated and is being signaled to grow (Dankel, Mattocks et al., 2017).

Taken together, the muscle activation strategy with low loads in combination with blood flow restriction appears to be distinctly different from that of traditional high-load exercise, which requires a high amount of muscle activation at the beginning of exercise in order to move the heavier load (S. B. Cook et al., 2013; Loenneke, Kim, et al., 2015). However, once the fiber is sufficiently activated, everything beyond that point appears to be similar between the two loading conditions. Evidence for contraction-induced metabolites inducing muscle growth, independent of mechanotransduction, is not currently supported by experimental evidence (Dankel, Buckner, et al., 2016). However, it is possible that there is an effect that is secondary to the powerful effects of muscle contraction. As such, future work could consider investigating this further. Importantly, future work should consider using time-matched non-exercise control groups in order to ensure that the change in any 'mechanism' of growth is due to the exercise intervention rather than some other factor (Hammert, Dankel, et al., 2024).

The mechanism(s) for the change in maximal strength are even less clear (Colomer-Poveda et al., 2017). Lower intensity/load exercise combined with blood flow restriction can improve maximal muscle strength over the same exercise without blood flow restriction (Loenneke, Fahs, Rossow, Abe, et al., 2012). However, the change in maximal muscle strength is almost always less than that of higher-load resistance exercise (Lixandrao et al., 2018). This is especially true if measured in the task that was specifically trained (Martin-Hernandez et al., 2013; Wong, Spitz, Song, et al., 2024). The reason for this change in strength is not known but classic exercise physiology would suggest that early changes are due to neural adaptations followed by large contributions from muscle hypertrophy (Ikai & Fukunaga, 1970; Moritani & deVries, 1979). Popular as it may be, the experimental support for that idea is lacking and more

recent work has failed to find an advantage of muscle growth for changes in muscle strength (Buckner et al., 2021; Dankel et al., 2020; Mattocks et al., 2017). Mediation analyses have also not found evidence that the change in muscle strength could be explained by changes in muscle size (Jessee et al., 2021; Spitz et al., 2023; Wong, Spitz, Bentley, et al., 2024). Part of this could be related to the noise associated with measuring physiological variables over time, but it might also be that exercise-induced skeletal muscle growth is either not a mechanism or plays only a small role for the change in strength (Loenneke, 2021; Loenneke et al., 2019). Other possible candidates could be alterations in output from the brain, less inhibition or great facilitation through the spinal cord, or alterations in the alpha motor neuron (Krutki et al., 2017; Siddique et al., 2020). There could also be alterations at the fiber level (Dankel et al., 2019), or at the level of the myosin head that might occur independent of a change in muscle size (Hammert, Kataoka, et al., 2023). Some have hypothesized that the disconnect between changes in muscle size and strength may be due to sarcoplasmic (i.e. disproportionately larger increase in non-force generating elements) rather than myofibrillar hypertrophy (Roberts et al., 2020). If that thesis is true, it could potentially explain the disconnect between muscle growth and changes in strength following low load training with blood flow restriction and high-load training. However, the sarcoplasmic hypertrophy hypothesis lacks experimental support and the current body of evidence argues that growth is the result of a proportionate increase in the force-generating and non-force generating elements (Jorgenson et al., 2020; Libardi et al., 2024).

Future experimental work, with proper controls, is necessary before we can delineate the strength change to exercise both with and without blood flow restriction. Moving beyond 'growth is detected', so it must be a mechanism or 'growth is not detected', so it is neural, will be paramount in meeting this goal. Statistical mediation is one approach (albeit with a host of assumptions) that could be used to help determine how much of an effect is driven by a third variable (e.g. changes in neural drive, changes in skeletal muscle size, etc.) (Hayes & Rockwood, 2017; Montoya & Hayes, 2017). Importantly, these training groups should be compared to a non-exercise time matched control group. The use of a time-matched non-exercise control group is necessary to evaluate whether the observed effect(s) were due to the training intervention (i.e. does signal exceed noise) (Hammert, Dankel, et al., 2024).

Are there sex differences in the effects of blood flow restriction?

Early work on blood flow restriction centered largely on men and there has been a focus on correcting this in the literature (Counts et al., 2018). When addressing this question, it is important to separate the main effect of sex from the actual moderating effect. For example, a main effect of sex would likely be seen in that females are generally weaker in terms of the absolute load lifted, whereas a moderating effect would be detected if the change in maximal strength following blood flow restricted exercise was influenced by sex (i.e. the relationship between training and strength change depended on

biological sex). The main effect is a difference that has nothing to do with blood flow restriction. Consideration will need to be given to the menstrual cycle and investigators will need to determine if or how they will control for the phase in which data is collected (Elliott-Sale et al., 2021). These studies will require a larger sample size (i.e. in order to be powered to detect a sex*treatment effect) than that required to simply test a treatment effect of blood flow restriction. Further, both sexes will need to be included in the same study and directly compared as opposed to 'this study with males saw a change, another study with females did not'.

Are the effects observed due to the pressure applied or the reduction of blood flow? Or does it depend?

Researchers have quantified the reductions in blood flow to the application of different relative pressures with and without exercise (Crossley et al., 2020; Mouser et al., 2017, 2018). This work is often used as evidence for why two pressures might be similarly effective if applied with training. However, this assumes that the effect is driven by the reduction of blood flow. This is reasonable, but it is also possible that the pressure itself, independent of the effect it has on flow, may be playing some role with adaptation. In humans, this is difficult to test, but some have approached this problem utilizing pressures that exceed arterial occlusion pressure (e.g. 100% AOP vs. 150% AOP) (Kataoka et al., 2024; Nucci et al., 2022). This theoretically results in similar reductions in blood flow and could allow for the testing of pressure. A possible limitation is that this requires supra-occlusive pressures. Finding creative designs to test this in humans could yield important insights into how blood flow restriction works and how it might differ based on the outcome measured (e.g. muscle size, strength, limb blood flow, pain sensitivity, bone, etc.).

Are there individual responses to blood flow restriction?

Addressing this question is more difficult than simply plotting the individual data and comparing change scores (Atkinson & Batterham, 2015; Dankel & Loenneke, 2020). The change scores within a training group are certainly not all going to be the same, but this in and of itself cannot be interpreted as being due to the intervention. Some researchers create thresholds based off of short-term reliability estimates. In other words, short-term test-retest reliability (i.e. 24–48 h) is used to set the bounds that should be exceeded in order to be considered a differential responder. However, there are various sources of error that must be accounted for in order to confidently identify individual responders. Only accounting for short-term measurement error will almost certainly underestimate the overall error and lead to spurious discussions of individual responders (Atkinson et al., 2015). Arguably the best way to address this question is by utilizing a replicate-crossover design (Robinson et al., 2024; Senn, 2024), whereby every participant completes the treatment and non-exercise control condition twice. For acute designs, this is easier to do because any acute effect of blood flow restriction would likely be washed out in a few days.

Studying chronic adaptations is more difficult, because the effects (e.g. strength) can stay elevated for extended periods of time post-training (Ogasawara et al., 2013). One way to approximate individual responses in this case is by comparing the standard deviation (SD) of the treatment group to the SD of a completely separate time-matched non-exercise control group (Atkinson & Batterham, 2015). If the SD of the change score is much greater than that of the non-exercise control, then that would provide some evidence that there could be individual responders to the treatment. The fundamental assumption inherent to this procedure is that the participants in the treatment and control groups differ only by the treatment they receive. In other words, it assumes that the within-subject variability does not differ between those randomized into the exercise and control groups. Nevertheless, investigating this question may eventually provide clues as to why some may respond differently than others and allow for interventions to be better tailored to those who may respond less. But, it will be important to confidently determine whether an individual response can be confidently detected prior to working on the question of 'why do some people respond differently?'.

Can blood flow restriction augment high-load exercise? Does it differ based on the outcome assessed?

Traditionally, it has been recommended that blood flow restriction be applied only with lower loads (Patterson et al., 2019). This is based on work which found that intermittent blood flow restriction was not able to augment adaptation in a limb training with a higher load (Biazon et al., 2019; G. Laurentino et al., 2008; Teixeira et al., 2021). The intermittent approach might be related to the discomfort associated with blood flow restricted exercise (Spitz et al., 2022), making it potentially difficult to complete the exercise with a higher-load in combination with continuous blood flow restriction, unless the prescribed repetitions are low (Hammert, Moreno, et al., 2023). However, what if blood flow restriction is applied to a limb that is not being exercised? Could the sensation of pressure in a non-exercised limb favorably impact a free-flow limb training with a higher load? There is some evidence to suggest that this is possible (C. J. Cook et al., 2014) but it is not well understood or generally accepted. Applying blood flow restriction to non-exercised limbs reduces the possibility that the exercising muscle stops exercising prematurely due to discomfort or metabolically induced contractile failure. Future work is needed to better address this question and determine what adaptations may or may not occur from applying blood flow restriction in this manner. For example, would blood flow restriction-induced improvements in resting limb blood flow be observed in a limb not undergoing restricted blood flow? Or, would the effects of applying blood flow restriction with high-load exercise be more likely to occur with outcomes like strength where the mechanism is likely to be more neural in origin? It might also be possible that the signal for strength gain from traditional high-load exercise is so large that it cannot be augmented to any appreciable degree.

What is the ideal approach for testing a treatment effect of blood flow restriction in combination with exercise?

The number of groups/conditions will depend upon the specific question of interest. Only two conditions/groups are needed if the question is whether exercise in combination with blood flow restriction can augment 'x' over the same exercise without blood flow restriction (Low-load vs. Low-load + Blood flow restriction). However, if the interest is to make a claim about the effect of exercise itself, then a non-exercise time matched control condition/group will also be required (Low-load vs. Low-load + Blood flow restriction vs. non-exercise time matched control). The control is often ignored in favor of looking at pre-post changes across time (or a time effect). However, it is difficult to make claims about exercise when all groups are exercising. A significant time effect can inform whether the average of 'x' differs between the pre- and post-time points, but it will not be known whether that difference was due to the exercise intervention itself (Hammert, Dankel, et al., 2024).

The complicated part of the study design comes with determining how to prescribe the workload (i.e. load, repetitions) with blood flow restricted exercise. In order to test the effect of blood flow restriction, the only thing that should differ between the two exercise groups is the application of blood flow restriction. One approach is to use goal repetitions, such as 30-15-15-15 across four sets of exercise (Yasuda et al., 2010). The potential issue with this approach is that it is not uncommon for this to turn into a failure protocol for some participants (Barnett et al., 2016; Jessee et al., 2017; Mouser et al., 2017). This is problematic in that groups/conditions start to differ by the number of repetitions performed as well as the application of blood flow restriction. This led to the recommendation that every group/condition should just exercise to failure (Dankel, Jessee, et al., 2017) so that effort could be standardized. However, this also leads to differences in workload which makes it difficult to know what effect blood flow restriction is having. Failure also creates a very large physiological perturbation which may largely saturate most of the signals necessary for adaptation. That is, the exercise is so powerful that it will be difficult or impossible (e.g. with outcomes like muscle growth) to see a benefit with blood flow restriction. We have recently implemented an approach that accounts for both of the aforementioned limitations. Specifically, we had individuals exercise to failure with low-loads (e.g. 30% 1RM) in combination with blood flow restriction on the initial visit to the laboratory and then prescribed a percentage of repetitions from each set (e.g. 70% of repetitions) for subsequent visits (Hammert, Song, et al., 2024; Yamada, Hammert, Kataoka, Song, Kang, Kassiano, et al., 2025). The utility of this approach is that it is submaximal and accounts for each individual's maximal strength and endurance capacity. This method is in its infancy and likely requires additional revision over time but might offer one method for better studying blood flow restriction in the future.

The final point about study design is whether to use a within-subject or between-subject design. Assuming an adequate wash-out between visits, a within-subject approach is likely favorable when studying the acute effects of blood flow

restriction (different conditions completed on different days). However, a between-subject design is likely superior for studying long-term adaptations. We traditionally used within-subject designs, because they are more statistically powerful (Bell, Wong, et al., 2020). We would apply one treatment to the right arm and another to the left arm (Buckner et al., 2020; Counts et al., 2016). This approach assumed that one limb training would not impact the other limb also training. Although the cross-education effect is well documented (Manca et al., 2017), it was hypothesized that this effect would not appreciably impact results when both limbs were training with different protocols (Bell, Wong, et al., 2020). However, we now have evidence that one limb training can indeed impact strength in the opposite limb training with a different protocol (Bell et al., 2023). Because of this, we recommend researchers to consider using between-subject designs in the future work studying adaptations across time. It may also be worth reviewing some of the findings based largely off of within-subject designs to determine if the conclusions drawn from them hold when removing the influence that one limb could have on another (e.g. influence of pressure on muscle growth (Counts et al., 2016; Lixandrao et al., 2015)).

Conclusion

In closing, the past 25 years of research on blood flow restriction have produced effective treatments that are being used to help people in the real-world (Castle et al., 2023). The findings discussed in this paper make it clear that blood flow restriction should not be dismissed as some fad nor should it be discussed as some idea that has just been recycled and repurposed from the past. Much is known about blood flow restriction, but there is still much to learn. Currently, there are more research groups studying blood flow restriction than at any other time in history (Feng et al., 2022). It is our hope that this paper has helped highlight what is known but also what can be further addressed in the next 25 years of blood flow restriction research. We highlighted the guidelines currently accepted for applying blood flow restriction in practice. These should be viewed as the best practices for applying blood flow restriction as of the year 2024 but should not necessarily be used to suppress researchers seeking to experiment with innovative methods for applying blood flow restriction. Theory and guidelines are vital, but they are not holy writ.

Acknowledgments

Images for Figure 1 were retrieved from the following:

Muscle image used courtesy of https://smart.servier.com/smart_image/muscle-2.

Dumbbell image used courtesy of <https://clipartstation.com/dumbbells-clipart-1-2/> in the year 2019.

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Pain sensitivity image courtesy of Pain: https://www.flaticon.com/free-icon/pain_927559?term=pain&page=1&position=14&origin=search&related_id=927559. Tendon stiffness image courtesy of https://smart.servier.com/smart_image/tendonitis/.

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Images for Figure 2 were retrieved from the following:

Muscle images used courtesy of https://smart.servier.com/smart_image/muscle-2.

Dumbbell image used courtesy of <https://clipartstation.com/dumbbells-clipart-1-2/> in the year 2019.

Sex symbol courtesy of https://www.flaticon.com/free-icon/sex_4252727.

The arm was used courtesy of <https://openclipart.org/detail/271117/human-arm>.

Individual stick people were used courtesy of <https://www.clker.com/clipart-stick-man-7.html>.

The individual lifting weights is a stock photo from our laboratory.

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