Physiology International 109 (2022) 2, 186–203
DOI: 10.1556/2060.2022.00223

AKADÉMIAI KIADÓ

A narrative review of the effects of blood flow restriction on vascular structure and function

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Received: December 18, 2021 • Revised manuscript received: March 10, 2022 • Accepted: March 22, 2022
Published online: May 18, 2022

ABSTRACT

Blood flow restriction is growing in popularity as a tool for increasing muscular size and strength. Currently, guidelines exist for using blood flow restriction alone and in combination with endurance and resistance exercise. However, only about 1.3% of practitioners familiar with blood flow restriction applications have utilized it for vascular changes, suggesting many of the guidelines are based on skeletal muscle outcomes. Thus, this narrative review is intended to explore the literature available in which blood flow restriction, or a similar application, assess the changes in vascular structure or function. Based on the literature, there is a knowledge gap in how applying blood flow restriction with relative pressures may alter the vasculature when applied alone, with endurance exercise, and with resistance exercise. In many instances, the application of blood flow restriction was not in accordance with the current guidelines, making it difficult to draw definitive conclusions as to how the vascular system would be affected. Additionally, several studies report no change in vascular structure or function, but few studies look at variables for both outcomes. By examining outcomes for both structure and function, investigators would be able to generate recommendations for the use of blood flow restriction to improve vascular structure and/or function in the future.

KEYWORDS

vascular adaptations, arterial occlusion, angiogenesis, arterial stiffness, flow mediated dilation, blood flow restriction

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INTRODUCTION

Blood flow restriction, as a therapeutic modality, refers to the application of a pneumatic cuff or restrictive device meant to reduce arterial flow and occlude venous flow within a limb [1]. Restriction is typically applied to the uppermost portion of a limb and based on recent guidelines, a relative pressure in the range of 40–80% of arterial occlusion pressure (AOP) should be applied [1]. Applying a relative pressure is meant to account for any individual differences across participants, cuffs, and devices [2, 3]. With pneumatic devices, relative pressures can be applied by inflating a pneumatic cuff on the limb until a pulse distal to the cuff is no longer present (i.e., AOP), then applying a percentage of that pressure for the therapy. This distinguishes blood flow restriction from other, somewhat similar modalities, such as ischemic preconditioning, which occludes both venous and arterial blood flow [4].

Blood flow restriction is, and has been applied in various ways, including alone, combined with endurance or resistance exercise, or in combination with other therapies, such as neuromuscular electrostimulation and whole body vibration. Additionally, the reasons for applying blood flow restriction may vary. In a survey of practitioners conducted in 2015, 32.6% of respondents reported (most common response) using blood flow restriction for the purpose of inducing muscle hypertrophy [5]. This is likely due to the large body of evidence suggesting that blood flow restriction alone can attenuate atrophy [6], while combining it with low intensity endurance exercise [7] and low load resistance exercise leads to hypertrophy [8]. Beyond muscular hypertrophy, the most common purposes of use for blood flow restriction were injury rehabilitation (24.2%), increases in muscle/bone strength (10.1%), and aerobic conditioning (1.8%) [5]. Interestingly, improving vascular function was the least common purpose for use, with only 1.3% of the 250 surveyed practitioners indicating this as their reason for using blood flow restriction [5]. The bulk of scientific literature investigating blood flow restriction seems to evaluate muscle size and strength outcomes. Recently, a push for blood flow restriction standardization has improved the reporting of various factors (i.e. cuff type, device used, intermittent or continuous cuff inflation, relative pressure applied, participant characteristics, etc.) that could influence different outcomes. Guidelines have been developed for the use of blood flow restriction alone, with endurance exercise, and with resistance exercise for eliciting improvements in muscle size, strength, and function [1].

However, there are no guidelines on the best way to improve vascular function or structure via blood flow restriction. To the best of our knowledge, the best way to improve vascular function has yet to be discovered. In fact, there is inconclusive evidence whether the potential therapy may produce beneficial vascular outcomes due to limited research on the topic. While there are previous reviews on this topic, they summarize the literature prior to important evolutions in its application, such as utilization of relative pressures, and did not include blood flow restriction applied without exercise [9–11]. Therefore, the purpose of this narrative review is to compare and contrast the current body of available literature investigating blood flow restriction as a therapy with indices of vascular function and structure as the main outcomes. We will review the state of the current evidence with different outcomes when blood flow restriction is applied alone, with endurance exercise, with resistance exercise, and with other therapies. Additionally, we will discuss potential avenues for future research.

MEASUREMENTS

Much of the blood flow restriction literature investigating vascular outcomes use non-invasive measures. For example, blood flow has typically been measured via ultrasonography [12, 13] and strain gauge plethysmography [14–16]. Using ultrasonography, blood flow is estimated based on artery diameter and blood flow velocity via B-mode imaging and pulse wave Doppler, respectively [13]. Strain gauge plethysmography estimates blood flow via changes in limb circumference (quantified via strain gauge) following a variety of cuff inflations proximal and distal to the assessed limb section, e.g., the forearm or calf. From this measure, vascular conductance [14, 16] and vascular resistance [14, 15, 17] can also be derived.

Pulse wave velocity, considered the gold standard for assessing arterial stiffness [18], is determined by quantifying the travel time of the pulse pressure wave generated by the cardiac cycle from one anatomical site to the next, made relative to the distance traveled [19]. Other methods, such as cardio-ankle vascular index [20–22] and ankle-brachial index [19–21, 23] have also been used for assessing changes in arterial stiffness. Lastly, endothelial function is often assessed via flow mediated dilation, using ultrasonography (mentioned previously) to quantify changes in blood flow and artery diameter following an occlusive stimulus [24]. The use of flow mediated dilation should follow the most current guidelines [25].

BLOOD FLOW RESTRICTION ALONE

While literature is available on the use of blood flow restriction alone as a therapy, most is focused on attenuating atrophy and losses in muscle strength [6, 26–28] and current guidelines suggest using higher blood flow restriction pressures of 70–100% AOP [1]. A recent study applying cyclic blood flow restriction at 100% AOP twice a day 5 days a week, to an immobilized limb, over 14 days, as a means to attenuate maladaptation to the vasculature, found no change in vascular function [29]. However, from this alone it is difficult to determine whether blood flow restriction is effective as neither the immobilized control group (maladaptation expected) nor the immobilized blood flow restriction group saw a change in flow-mediated dilation. As one of the first chronic studies to investigate the vascular changes to blood flow restriction alone, we should consider that if an effect did exist there may have been a lack of power to detect it (small sample size). Aside from this study, information on blood flow restriction alone as it relates to chronic effects on vascular function and structure are lacking. However, the literature on enhanced external counterpulsation and ischemic preconditioning may be useful to compare the possible effects of blood flow restriction alone. Enhanced external counterpulsation involves the use of multiple cuffs being sequentially inflated on the limbs, in sync with the cardiac cycle. Typical application is for the treatment of coronary artery disease and unstable angina [30]. For example, in patients with chronic stable angina, about a month of treatment with enhanced external counterpulsation improves exercise tolerance, possibly due to decreased peripheral resistance [31]. Vascular health benefits may be realized in healthy populations as well, evidenced by acute application of enhanced external counterpulsation improving endothelial function, in both the femoral and brachial arteries [32]. Ischemic preconditioning is a method of applying an occlusive stimulus to a limb, and after a period of ischemia, allowing reperfusion. A typical ischemic preconditioning cycle would be completed by inflating a cuff on the limb to

an absolute pressure of 220 mmHg for 5 min and then deflating the cuff for 5 min [4]. An 8 week study of ischemic preconditioning showed improved endothelial function after the initial 2 weeks, but no microcirculation or artery diameter changes [4]. Also, using 4 bouts of occlusion/perfusion cycles daily for 1 week increased forearm vascular conductance and flow mediated dilation in both the treated and contralateral arm, and remained elevated 1 week after the intervention [33]. After 4 weeks of daily ischemic preconditioning resting blood flow does not appear to change, although vascular endothelial growth factor (VEGF) and the number of endothelial progenitor cells increased in both the arm receiving the stimulus and the arm without [34]. Increases in these markers could be indicative of angiogenesis and other vascular changes with an extended program beyond 4 weeks, but this was not investigated.

From current research it would seem that the application of blood flow restriction alone would not improve endothelial function when applied at an ischemic pressure [29]. However, it is not clear how the chronic or acute changes when using higher or lower relative pressures would differ from enhanced external counterpulsation and ischemic preconditioning. Blood flow restriction alone, as a therapy, has generally been applied by inflating a single cuff on the proximal portion of a limb for 5 cycles of 5 min each separated by 3 min of deflation [6, 26–28]. Enhanced external counterpulsation, in contrast, involves pulsed inflations of multiple cuffs on both distal and proximal portions of a limb to diastolic blood pressures, for up to an hour. This pulsatile inflation method is used to promote venous return to the heart, while typical blood flow restriction application is used to reduce arterial blood flow in a limb and restrict venous return [35, 36]. Additionally, while ischemic preconditioning is meant to induce a period of ischemia (no blood flow) followed by full reperfusion of the limb, blood flow restriction typically reduces arterial blood flow. Therefore, while each of the three therapies use cuffs to apply external pressure around the limb, the resulting stimuli are different and may induce discrepant adaptations.

When investigating the effect of blood flow restriction alone on vascular function, a decrease in venous compliance was found after acute application [37]. Whether this was a normal transient response post-treatment with blood flow restriction, or whether there are long-term implications requires more investigation. Further insight into the possible effects of blood flow restriction alone on vascular function may come from the acute neurohormonal and oxidative stress responses. However, even these implications seem inconclusive as they relate to long-term adaptations. To illustrate, norepinephrine, vasopressin, and plasma renin activity increase in response to blood flow restriction being applied to the legs while supine [36, 38] and during head-down 24-h bedrest [39], but norepinephrine [40] and plasma renin activity [41] may be associated with decreased vascular function while vasopressin is associated with greater vascular function [42]. It should also be noted that the effect of blood flow restriction alone on this hormonal response has only been investigated acutely, and the effect is comparable to the response seen with the transition from lying down to standing upright [38], thus, the overall effectiveness of such a therapy, if there is one, may also depend upon the baseline health of the population to which it is applied.

In addition to hormones, other signaling molecules like reactive oxygenated species are linked to VEGF and can increase endothelial cell migration [43] which is essential for angiogenesis and vascular remodeling [44]. When comparing blood flow restriction alone to exercises with (low load) and without blood flow restriction (low load as well as high load), reactive oxygenated species increased in all conditions except low load without blood flow restriction

[45]. Reactive oxygenated species can be stimulated by shear stress and may have an effect on vascular adaptations; however, it appears that shear stress may also promote positive structural changes in the endothelial cytoskeleton as speculated in a review by Zhang and Gutterman [46]. When measuring blood flow and shear rate (shear stress without a measure of blood viscosity) at increasing relative pressures, shear rates decline at a similar rate as blood flow [47]. This could suggest that using higher relative pressures would be less likely to stimulate changes in endothelium structure compared to moderate or lower relative pressures. However, due to the underreported nature of resting shear rate and blood flow in the blood flow restriction literature, the current evidence on the effect of blood flow and shear rate on endothelial function across different pressures is weak. Further, there are some arguments about the different types of blood flow profiles and how they may impact acute and chronic vascular changes. For example, some authors suggest that increases in retrograde shear stress [48, 49] and oscillatory shear [50, 51] may impair endothelial function. Interestingly, acute bouts of retrograde blood flow, which peaks between relative blood flow restriction pressures of 30% AOP and 60% AOP [52], may improve endothelial function [32]. Based on the acute investigations of reactive oxygenated species and components of blood flow, it is not clear whether the acute responses to blood flow restriction alone would translate to vascular changes when a relative pressure is applied chronically. Since only one long-term study has been conducted to investigate the effects of blood flow restriction alone on vascular function, it is unclear whether a blood flow restriction protocol alone would result in similar positive adaptations as enhanced external counterpulsation and/or ischemic preconditioning, negative adaptations, or no adaptations at all. Furthermore, it is unknown what role variables such as stimulus frequency, applied pressure, and inflation duration would play. This is an area in need of further investigation.

BLOOD FLOW RESTRICTED ENDURANCE EXERCISE

Traditionally, endurance exercise performed at moderate-vigorous intensity is used to improve a myriad of outcomes such as cardiometabolic health and cardiorespiratory fitness [53]. When combining blood flow restriction with endurance training at low intensities, similar outcomes have been observed, albeit not conclusively. When compared to non-restricted walking, blood flow restriction combined with walk training improves muscle size and muscle strength in elderly adults [7], and anaerobic power, cardiorespiratory fitness, and minute ventilation in athletes [54]. Additionally, in physically active men, a training protocol combining blood flow restriction with 15 min of cycling at light intensity increased cardiorespiratory fitness after 8 weeks compared to 45 min of cycling at the same intensity without blood flow restriction [55]. However, in recreationally active males, vigorous cycling for 20 min three times a week over 6 weeks did not differ in cardiorespiratory fitness when compared to light cycling with blood flow restriction or a non-exercise control [56]. Though these studies varied in their determination of light intensity, they fell within a predetermined range of 30–39% of heart rate reserve and 37–45% of maximal oxygen uptake. Discrepancies between the outcomes could be due to the cycling training period, duration of the training sessions, or the frequency of the protocol was perhaps not enough for that time frame as Park et al. [54] found cardiorespiratory fitness improvements with light intensity walking sessions twice a day. Another

consideration for changes in oxygen uptake is exercise intensity. For example, performing intervals at a higher intensity of 80% peak running velocity just twice a week improved cardiorespiratory fitness in both the blood flow restriction group and the control group after 4 weeks [57].

As it pertains to vascular function, 5 sets of walking for 2 min at 2 mph combined with blood flow restriction seems to acutely decrease popliteal artery endothelial function 20 min post-exercise when compared to a non-restriction condition [58], suggesting that blood flow restriction combined with walking may be detrimental to vascular adaptations long-term. However, with chronic walk training, the addition of blood flow restriction does not seem to be detrimental when compared to walking alone. Following 10 weeks of walk training with and without blood flow restriction, elderly men had similar improvements in carotid arterial compliance between the two conditions [59]. Although blood flow restriction did not augment adaptations in carotid arterial compliance, it was not detrimental either. Six weeks of cycling with one leg under blood flow restriction and the opposing leg unrestricted, resting femoral diameter [60] and femoral blood flow during exercise [61] only increased in the blood flow restricted leg when compared to pre-training. Additionally, when compared to a non-exercise control group, elderly women saw improvements in venous compliance of the legs, but not in the arms, after 6 weeks of blood flow restriction walking, suggesting a localized positive effect of this modality [62]. It should be noted, this adaptation was not compared to walking alone, so it remains unknown whether the adaptation was attenuated, augmented, or unaffected by the addition of blood flow restriction. Six weeks of cycling with low intensity blood flow restriction has also led to no change in carotid-radial pulse wave velocity, or carotid-femoral pulse wave velocity, but did lead to a localized improvement in femoral-tibial pulse wave velocity [63]. However, this localized change in femoral-tibial pulse wave velocity did not differ among blood flow restriction exercise, a non-exercise control, or high intensity exercise. Over 12 weeks, older trained males had an increase in flow-mediated dilation in the brachial and popliteal arteries using high intensity cycling with blood flow restriction, high intensity cycling alone, and a non-exercise control group [64]. When comparing the acute responses to those seen chronically, we explore possible reasons for the conflicting results. First, acute changes in vascular function may not be reflective of chronic changes. Second, the exercise protocol used by Renzi et al. [58] comprised 5 sets of walking for 2 min, separated by 1 min of rest, which is half of the overall duration per session of the chronic studies which employed 20 min of continuous walking with no rest [59, 62]. Third, although the background activity level of participants was not thoroughly described, a 2 mph walking speed for a younger active population [58] may not be an adequate stimulus, with or without blood flow restriction, when compared to ~2.5 mph for sedentary elderly males [59] and females [62].

Based on the current research, there does not seem to be definitive evidence that blood flow restriction application combined with low intensity endurance training augments or attenuates adaptations in vascular function. However, chronic evidence does seem to suggest that the combination of modalities is not detrimental. Current recommendations for applying blood flow restriction with endurance exercise may lead to clearer outcomes with future research [1]. More research should be conducted to determine whether this type of training only improves vascular function for elderly and/or sedentary populations and if there is an optimal relative intensity, frequency, minimum exercise training period, or a specific modality of endurance exercise that is most beneficial.

BLOOD FLOW RESTRICTED LOW LOAD RESISTANCE EXERCISE

As mentioned previously, the majority of literature examining the effects of blood flow restriction investigate outcomes of muscle size and strength. This is likely due to the accumulation of evidence showing that a similar hypertrophic response to traditional high load resistance training and resistance training with low loads alone can be achieved at a lower workload when low load resistance training is combined with blood flow restriction. To illustrate, blood flow restriction training with 15% of their one-repetition maximum (1RM) and 40% AOP results in similar muscle growth as training with 70% 1RM for 8 weeks [65], making blood flow restriction training an attractive alternative for those that may be injured or averse to high loads. While low load training alone also results in a similar muscle hypertrophic response as high load training, it is predicated on exercising to momentary failure [66, 67], which may cause the volume of work to become quite tedious. Adding blood flow restriction to low load training reduces this workload while resulting in similar outcomes [8, 65, 68]. However, while blood flow restriction is touted as a viable modality to achieve muscle growth, less overall is known about the effects on the vascular system. A recent meta-analysis found no difference in vascular function between traditional high load exercise and blood flow restriction exercise [11]. However, low load resistance exercise may have greater enhancements in endothelial function when compared to low load exercise alone [11]. There has been a recent push to standardize blood flow restriction application [1], but due to differences in methodology of current literature, there are a limited number of studies available to make direct comparisons about vascular adaptation as we described below.

Blood flow

A whole body resistance training protocol using high loads can elicit increases in resting brachial artery diameter and peak post-occlusive blood flow after 6 and 12 weeks of training, albeit without concomitant changes in flow mediated dilation [69]. After 4 weeks of low load blood flow restriction training using either 25% 1RM or 50% 1RM, peak post-occlusive blood flow increased over repetition matched conditions using the same loads without restriction [70]. Additionally, 4 weeks of progressive heel raises led to improved calf filtration capacity in the blood flow restricted leg when compared to the non-restricted leg [71]. However, these results should be interpreted with caution, as these non-restricted protocols [70, 71] were volume matched to their respective blood flow restriction conditions. Thus, the strength of the stimulus may be lower for the non-restricted conditions as the application of blood flow restriction has been shown to reduce the amount of work an individual can perform before reaching momentary failure [72], which is indicative of a greater stressor. Therefore, it is difficult to determine whether blood flow restriction improves vascular function to a greater degree than low load exercise alone if the non-restricted condition is work-matched to the restricted condition. In fact, 6 weeks of training with 30% 1RM to momentary failure with and without blood flow restriction resulted in increased vascular conductance following the non-restricted condition only [23]. The lack of responsiveness in vascular conductance following blood flow restriction training may have been due to the confounding effects of participant age (mean = 55 years) and/or greater pre-training values of vascular conductance in the blood flow restriction condition rather than suggesting blood flow restriction is ineffective. For example,

improvements in vascular conductance for young adults (mean age = 21 years) following training with blood flow restriction (20% 1RM) for 6 weeks were similar to non-restricted training with 70% 1RM and 45% 1RM [14]. Additionally, Mouser et al. [16] suggest adaptations may be dependent upon restriction pressure after finding that increases in vascular conductance following training with 15% 1RM combined with 80% AOP to be similar to traditional high load training, while training with 15% 1RM alone or 15% 1RM combined with 40% AOP did not change vascular conductance. Although Fahs et al. [23] investigated the effects of a relative pressure, most others did not, using a single absolute pressure instead. Therefore, much more should be investigated regarding the effects of different relative pressures on outcomes of vascular conductance and blood flow.

Evidence also suggests that changes in measures outside of resting values should be considered. As mentioned previously, Patterson and Ferguson [70] found changes in peak post-occlusive blood flow, however, the authors did not observe any changes in resting measures of blood flow. Similarly, Hunt et al. [73] found no changes in resting blood flow over the course of 6 weeks of blood flow restriction training nor traditional resistance training. The authors did observe changes in flow mediated dilation and peak diameter following a period of ischemia [73]. Thus, changes in resting blood flow velocity alone should not be the sole indicator used to assess vascular adaptation in future studies. Using multiple different measures to assess vascular function would provide a larger representation of the changes that occur with different training modalities and allow for more in-depth comparison across studies.

Arterial stiffness

Arterial stiffness has been reported to increase with traditional high load resistance training [74] though conflicting arguments have since reported no effect on arterial stiffness [75]. With low load blood flow restriction exercise, most studies have indicated no change in arterial stiffness. Neither 3 weeks of low load blood flow restricted knee extension, flexion, and leg press [76], nor 4 weeks of low load blood flow restricted bilateral knee extension changed measures of arterial stiffness [19]. In the upper body, 6 weeks of bench press training, using 30% 1RM with blood flow restriction and absolute pressures of 100–160 mmHg, also did not change arterial compliance (a measure of arterial stiffness) [77]. In contrast to these previous studies, Fahs et al. [23] observed an increase in arterial stiffness following 6 weeks of blood flow restricted unilateral knee extension training. The authors discuss how participant age (40–64 years) could be a driving factor, as arterial stiffness increases with age [23]. However, a separate study, also in older adults (61–85 years), found that 12 weeks of blood flow restriction training did not elicit observable changes in arterial stiffness [20]. Aside from the different exercises performed, it is difficult to determine why these studies observed different outcomes. Fahs et al. [23], Ozaki et al. [77] and Yasuda et al. [20] all used progressive pressures, and although these studies used different measures of arterial stiffness, pulse wave velocity and ankle-brachial index are strongly correlated and both are used to quantify coronary artery disease risk [78]. Of note, Fahs et al. [23] also saw increases in arterial stiffness following training in the leg without blood flow restriction. The authors noted a correlation between higher baseline pulse wave velocity values and the increase in pulse wave velocity after training [23]. Though the participants with a higher pulse wave velocity may have had a greater increase after training, it may be possible that these statistically significant changes are not clinically significant. A review on the clinical application

of arterial stiffness suggests that a pulse wave velocity of 18 m s^{-1} would require treatment, and if both limbs are less than 18 m s^{-1}, but one is more than 14 m s^{-1}, this would indicate a high risk for hypertension onset [79]. However, the pre- and post-training mean pulse wave velocity for Fahs et al. [23], for both conditions, was less than 10 m s^{-1}, and the mean change in the blood flow restriction condition was 0.6 m s^{-1}. Thus, neither training condition seems to exacerbate pulse wave velocity to a level of clinical risk. However, whether the level of pressure, progression of pressure, and/or duration of training would alter these changes in arterial stiffness remains to be investigated.

Endothelial function

The effects of a shorter-term blood flow restriction training protocol on endothelial function are conflicting. After 4 weeks of bilateral handgrip exercise with blood flow restriction, endothelial function decreased from baseline when compared to traditional exercise [51]. After 3 weeks of low load blood flow restricted knee extensions, flow mediated dilation decreased when compared to a non-exercise control leg [80]. However, Hunt et al. [24] observed improvements in both endothelial function and artery structure following 2 and 4 weeks of low load handgrip exercise with or without blood flow restriction. Of note, both adaptations returned to baseline after 2 weeks of detraining [24]. Similarly, reactive hyperemia index (a parameter of vascular endothelial function) improved to a greater extent with low load blood flow restriction exercise when compared to low load exercise without blood flow restriction [81]. There are a few things to consider when comparing these studies, Credeur et al. [51] had participants exercise under blood flow restriction for 20 min at 60% of their maximum voluntary contraction which is both a higher load and duration compared to the protocol by Hunt et al., which used 40% 1RM for 8.5 min [24], Bond et al. where individuals completed 12 repetitions with 30 s of rest while the cuff was inflated [80], or Shimizu et al. with 20% 1RM [81]. As speculated by Hunt et al. [24], a longer duration of blood flow restricted exercise may generate more reactive oxygenated species, decreasing nitric oxide availability necessary for functional adjustments in the artery [82]. It is also difficult to evaluate the restriction stimulus applied by Credeur et al. [51] as the authors used an absolute pressure of 80 mmHg on the distal portion of the upper arm and did not report cuff width.

Longer duration (i.e., >4 weeks) investigations of blood flow restriction training seem to show mixed effects on endothelial function. For example, when training over 8 weeks, flow mediated dilation improved with low load blood flow restriction and traditional high load when compared to no exercise [83]. Low load blood flow restriction has also been shown to improve flow mediated dilation when compared to high loads without blood flow restriction [84]. In contrast, during 8 weeks of wrist and arm exercises with and without blood flow restriction, chronic kidney disease patients saw increases in artery diameters, but this was not accompanied by any changes in endothelial function measured pre- and post-training [12]. Similarly, in an older but otherwise healthy population, there were no changes in endothelial function following 12 weeks of blood flow restriction training [20], nor from 12 weeks of detraining [21]. From these studies, one may speculate that intensities may not be high enough to elicit vascular adaptation, as noted by the large range in ratings of perceived exertion, reporting as low as 8 (very light) to as high as 14 (more than somewhat hard). However, the progressive increase in absolute cuff pressure may also lead to ischemic exercise in the last weeks of training, thus

making it difficult to determine the effects of blood flow restriction training. Additionally, if investigators are only measuring endothelial function and not changes in arterial structure, then vital information about vascular adaptations could be missed. We may not have a full representation of the possible changes that blood flow restriction training [20] or detraining [21] induce in the artery since artery structure was not measured.

When considering changes in endothelial function, one must also consider the timing of multiple assessments, as changes in endothelial function may be transient, returning to baseline levels once the structure of the artery changes [85]. With repeated stimuli to the vasculature, improvements start with artery function, but when artery structure changes then functionality may return to baseline values [85–87]. Thus, outcomes of endothelial function and structural changes of the artery can be difficult to compare across studies if assessments are not made often or if only one of these two factors are considered. Based on what we understand about the changes in arterial function and structure, we would expect that if there were no changes in flow mediated dilation, then structural changes may have likely occurred. This could be the case for some of the studies mentioned so far, based on a time course of vascular adaptations following blood flow restriction training, flow mediated dilation increased at week 2, was sustained at week 4, then returned to baseline at week 6 [73]. One possibility for flow mediated dilation returning to baseline at week 6 could be due to an increase in resting artery diameter (though not statistically significant in the study by Hunt et al.), increasing the stimulus threshold necessary to elicit an endothelial response. Although flow mediated dilation returned to baseline at week 6, maximum artery diameter following ischemic exercise increased from baseline. Thus, there does seem to be some improvements in the vascular response from blood flow restriction training even though there were no changes in resting diameter (artery structure) when training with or without blood flow restriction [73].

POTENTIAL MECHANISMS

Although the blood flow restriction literature lacks long-term studies linking mechanisms to vascular adaptations, acute investigations may provide some insight into long-term adaptations. Previous research has investigated the effects of nitric oxide [88] and mitogen-activated protein kinases in response to metabolic stress [89]. For the purposes of this review we will focus on the response of VEGF for the potential signaling of blood flow restriction to induce positive effects on vascular health. Takano et al. [90] observed increased plasma concentrations of VEGF, insulin-like growth factor 1, and lactate immediately, 10 min, and 30 min after bilateral knee extension exercise using low loads combined with blood flow restriction. Patterson et al. [91], also observed increased plasma VEGF at 30 min as well as 1 and 2 h after unilateral knee extension exercise with blood flow restriction, a change that was greater with blood flow restriction exercise than exercise without. Using bilateral knee extensions with the same pressure and cuff size as Patterson et al. [91], blood flow restriction exercise led to greater mRNA expression of VEGF 2- and 4-h post-exercise, hypoxia-inducible factor 1-α (HIF-1α), a VEGF regulator, at 2 h post-exercise, and VEGF receptor 2 at 4 h post-exercise when compared to the same exercise without blood flow restriction [92]. Larkin et al. [93], in assessing mitochondrial mRNA expression of VEGF, found VEGF and VEGF receptor 2 are higher under blood flow restriction at 4- and 24-h post-exercise, with HIF-1α higher at 4 h when compared to no blood

flow restriction [93]. However, serum VEGF may be greatest soon after exercise [90], and this may support the lack of change in plasma concentrations of VEGF and muscle VEGF protein from baseline when taken 4 or 24 h after exercise [93]. Based on the existing body of acute literature, blood flow restriction application seems to enhance markers for angiogenesis when compared to low load exercise alone, but the application of blood flow restriction in many of these studies was not made relative to the individuals participating, as suggested by Patterson et al. [1]. Thus, we do not know whether the application of different relative pressures (low, moderate, high) would have greater or lesser responses for these markers of potential adaptation.

MISCELLANEOUS

In some cases, blood flow restriction is combined with therapies such as whole body vibration [94–97], electrical stimulation [98], and passive movement [99]. While the primary outcomes of these studies are also mainly muscle size and function, we believe these studies are important to discuss as they may aid in the development of investigations into the effect of blood flow restriction combined with other therapies on vascular adaptations. Blood flow restriction and passive movement reduce atrophy and strength loss in bedridden patients, but may also show promise for vascular adaptation [100]. Acutely, blood flow restriction, with or without passive movement of a limb, stimulates a similar hypoxic environment at multiple tissue depths in the lower body musculature [99] and although deoxygenated hemoglobin is not an indicator of angiogenesis, a hypoxic environment may help stimulate the signaling cascade for angiogenesis [101].

An 8 week training program with whole body vibration (4 mm, 26 Hz) and blood flow restriction (pressure based on limb circumference) in a static squat position demonstrated improvements in muscle endurance [97]. This increase in muscular endurance could be due to an increase in VEGF and maximum heart rate when compared to whole body vibration alone [96]. In fact, 5 weeks of training with whole body vibration (amplitude not reported, 30 Hz), exercise (squats and heel raises), and blood flow restriction (highest pressure tolerated) combined, increased capillarity compared to a non-exercise control group [94]. While exercise alone would also increase capillarity, the addition of blood flow restriction (at the highest tolerable pressure) and whole body vibration does not seem detrimental to the vasculature, acutely. This protocol also seems to elicit increases in VEGF when compared to resting or resistance training alone, though HIF-1α did not differ [95]. Thus, whole body vibration and blood flow restricted exercise may induce a VEGF response independent of HIF-1α, which supports the increase in capillarity noted by Item et al. [94]. From these chronic and acute studies, it does seem that the addition of whole body vibration to blood flow restriction exercise may improve vascular function and potentially structure (not measured) by increased VEGF responses. However, there are no standard guidelines with this type of training, and the combination of equipment may be quite cumbersome. Thus, further research would need to be done to isolate the effects of different variables (e.g., vibration frequencies and amplitudes, restriction pressures, and resistance loads) before providing recommendations to clinicians.

A third therapy that has been combined with blood flow restriction is neuromuscular electrical stimulation, which has led to increased muscle strength [102], but the effects on vascular function are less known. In a study investigating the effect of neuromuscular electrical

stimulation and blood flow restriction, endothelial function improved in incomplete spinal cord injury patients following an acute 5 min application [98]. However, this acute increase in vascular function, when compared to blood flow restriction alone did not lead to improved functionality of the arm long-term (6 weeks of bi-weekly training). With this application, the electrical stimulation applied varied widely with a standard deviation of about 50 mA for each visit, potentially due to each individual's spinal cord classification or tolerance to electrical stimulation. In this case, blood flow restriction application was intended to induce ischemia by applying 130% of brachial systolic blood pressure to the upper arm. Following 14 days of limb immobilization, neither the use of blood flow restriction (100% AOP) alone or combined with electrical stimulation alter vascular function [29]. However, this study may not have been powered to detect any difference in endothelial function evidenced by the control group not having an expected decrease in endothelial function. Though there are not guidelines in place for blood flow restriction application in combination with neuromuscular stimulation to improve vascular function, inducing ischemia is not representative of the other blood flow restriction guidelines [1]. From these studies, there is room to build upon whether blood flow restriction and electrical stimulation could improve vascular function over a period of time and whether this would occur in other populations. The addition of electrical stimulation to blood flow restriction may enhance the stimulus necessary for improvements of arterial structure and function by inducing greater metabolic stress from muscle excitation. Thus, future research may investigate how different levels of electrical stimulation in addition to blood flow restriction may alter vascular adaptations.

CONCLUSIONS

Based on the current body of evidence, further research is necessary to determine whether blood flow restriction does improve vascular function, as well as guidelines for best practice. With blood flow restriction alone, future studies should investigate how much pressure should be applied and whether specific inflation and deflation periods are necessary to simulate the shear stress one would expect from exercise. Combined with endurance exercise, it remains to be seen whether effects are population, intensity, and/or modality specific. For improvements in vasculature with resistance training and blood flow restriction, future studies should investigate the influence of higher relative pressures and more frequent applications with a low to moderate load. Blood flow restriction application with other therapies needs further research to determine the best methods of applying blood flow restriction to improve vascular function, but when combined with whole body vibration, blood flow restriction seems to increase angiogenesis. All studies investigating changes in vascular function and structure should include several outcome variables (e.g., artery diameter, flow mediated dilation, ankle-brachial index) that could provide a better idea of the adaptations based on the time course of changes in the vasculature.

ACKNOWLEDGMENTS

The authors have no acknowledgments.

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