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A systematic review
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Low-intensity resistance exercise with blood flow restriction and arterial stiffness in humans: a systematic review

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Abstract

Low-intensity resistance exercise with blood flow restriction exercise is an emerging type of exercise recognition worldwide. This systematic review evaluated the effects of low-intensity resistance exercise performed with concurrent blood flow restriction (LIRE-BFR) on acute and chronic measures of arterial stiffness in humans. A systematic search in six healthcare science databases and reference lists was conducted. Data selected for primary analysis consisted of post-intervention changes in arterial stiffness markers. This systematic review included randomized and non-randomized controlled trials of LIRE-BFR in humans. Results: 156 articles were initially identified, 15 of which met inclusion criteria. Ten studies were excluded because they did not match predefined arterial stiffness markers. Thus, five articles were included in this review: two acute studies (N=39 individuals, age=20-30-years old, 30.8% women and 69.2% men) and three longitudinal studies (N = 51 individuals, age = 24-86-years old; 41.2% women and 58.8% men). Acute LIRE-BFR demonstrated both positive and negative effects on arterial stiffness in healthy young people. In contrast, longitudinal studies reported neutral effects in healthy young and older people. In conclusion, LIRE-BFR applied to the upper and lower limbs may acutely induce increases in central blood pressure and pulse wave velocity in healthy young people, whereas LIRE-BFR for the lower limbs may elicit positive effects related to indirect markers of arterial stiffness. Moreover, longitudinal LIRE-BFR studies showed no changes in arterial stiffness in young and older people. Hence, LIRE-BFR should be prescribed with a degree of caution to avoid non-intended responses in arterial stiffness markers in humans.

Key words: blood flow restriction; resistance exercise; arterial stiffness

1. Introduction

Low-intensity resistance exercise with blood flow restriction (LIRE-BFR) involves the occlusion of venous return using flexible cuffs or straps applied on the limbs.
to elicit skeletal muscle adaptations (i.e. hypertrophy, strength and muscular
endurance) (1). Traditionally, LIRE-BFR utilizes low loads (20-30% of one
maximum repetition, 1RM) and short rest periods, with some evidence showing
similar gains in muscle mass and strength compared to high-load resistance
exercise (2-6). Also, LIRE-BFR can be utilized in individuals recovering from joint
injuries (7) and patients undergoing cardiac rehabilitation (8). However, the
prescription of LIRE-BFR does not typically consider the potential for concomitant
cardiovascular and hemodynamic stress that may increase the risk of adverse
events during or post-application.

Some studies have shown LIRE-BFR promotes acute impairments on
hemodynamics, causing an increase in systolic and diastolic blood pressures,
particularly in elderly and hypertensive patients (9, 10). However, in these clinical
populations, autonomic cardiovascular (ACV) regulation are already altered (11).
The mechanisms that regulate the ACV are the arterial baroreflex, central
command, and the skeletal muscle exercise pressor reflex (SMEPR) (12). During
LIRE-BFR, central command and the SMEPR are activated. Also, neural signals
from central command recruit motor units for muscle contraction and stimulate
ACV regulation areas in the brainstem. The activation of sensitive skeletal muscle
afferent neurons (metaboreflex and mechanoreflex) regulates the SMEPR that
stimulates the brainstem areas (13). Thus, sensory information to the central
nervous system controls the efferent responses to the cardiovascular system.

Normally, LIRE-BFR induces an increase in sympathetic nerve activity and
decrease in parasympathetic nerve activity which are modulated by the arterial
baroreflex (14). Thus, these autonomic responses increase heart rate, cardiac
output, cardiac contractility and blood pressure (13). As a result, these
hemodynamic changes promote an elevation in arterial resistance and reduction
in venous capacitance (15).

Indeed, local accumulation of metabolites from LIRE-BFR could explain greater
activation of the sympathetic nervous system and adrenergic neurotransmitter
release, increasing both central (i.e. aortic and carotid) and peripheral (i.e.
brachial) blood pressures and arterial stiffness (16). Although acute LIRE-BFR
could impose elevated stress on the hemodynamic system, studies focused on
quantifying long-term changes are scant.

Acute and chronic changes in central arterial stiffness can be measured using a
variety of techniques. These techniques provide both direct (i.e. pulse wave
velocity, PWV) and indirect (i.e. central systolic and diastolic blood pressure,
cSBP/cDBP and augmentation index, AIx measures of the degree of stiffness
present in the radial and carotid arterial supply. Given that aortic hemodynamic
(central blood pressures) changes are predictive of cardiovascular disease (CVD)
(17), it becomes essential to understand how LIRE-BFR affects arterial stiffness
in humans to allow for safe prescription of this method, particularly in patients
with CVD and associated co-morbidities. Thus, the purpose of this paper was to
review the available literature on the acute and chronic effects of LIRE-BFR on
arterial stiffness in humans, and to draw evidence-based conclusions as to its
application across populations. We hypothesized that LIRE-BFR would have
negligible effects on central markers of arterial stiffness similar to traditional strength training.

2. Methods

2.1 Search Strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. An initial search was carried out on the following six databases: MEDLINE via Pubmed, EMBASE via Ovid, CINAHL (including pre CINAHL) via EBSCO, Web of Science, Sports Discus via EBSCO and the Cochrane Central Register of Controlled Trials. No restrictions were made for language. Variations of the following search terms were used: blood flow restriction, exercise modality and arterial stiffness (Figure 1).

2.2 Eligibility criteria

Our inclusion criteria were based on the PICOS criterions (P: participants; I: intervention; C: comparison; O: outcomes; S: study design). The details of inclusion criteria are as follows: (1) P: humans with mean ages ≥ 18 years; (2) I: the experimental group performed LIRE-BFR, control group or limb performed resistance exercise; (3) C: low-intensity resistance exercises or high-intensity resistance exercise; 4) O: the markers used in the included papers to evaluate the effects of LIRE-BFR on arterial stiffness were: cardio-ankle vascular index (CAVI), ankle brachial index (ABI), central systolic blood pressure (cSBP), central diastolic blood pressures (cDBP), central mean arterial pressure (cMAP), augmentation pressure (AP); augmentation index (Alx), augmentation index corrected by 75 bpm (Alx75) and pulse wave velocity (PWV) of acute and longitudinal studies ≥4 weeks; (5) S: randomized controlled trials (RCTs) and non-randomized controlled trials (NRCTs). Therefore, unpublished data, letters to the editor, theses, case reports, and review articles were excluded from the analysis along with any studies without a control group.

2.3 Selection of studies and data extraction

After the computerized search, the abstract and titles of all retrieved articles were screened by two of the authors (NR and SA). These authors reviewed relevant articles, determined study eligibility, and then extracted data on the study characteristics and endpoints. The study characteristics recorded were study design, description of intervention, outcome measures, and summary of main findings.

2.4 Assessment of included study quality

As per the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (18), risk of bias was assessed using seven explicit criteria that were individually rated for each study by the principal author (SA). In this context, selection bias, performance bias, detection bias, as well as attrition and reporting
bias were considered by the reviewer. Additionally, to assess the evidence of publication bias, funnel plots were visually inspected for each outcome criterion.

3 Results

3.1 Literature search

A comprehensive search of databases and in additional sources revealed a total of 156 articles. After removal of duplicates, the 41 remaining articles were submitted to an analysis of title and abstract along with relevant modality of exercise (resistance exercise). From these articles, 26 were considered to be potentially eligible for further review. After full-text review, 14 articles were excluded based on the modality of exercise, 5 were excluded based on arterial stiffness parameters required and 2 studies were excluded based on study design without control group, leaving 5 articles for review. Subsequently, a systematic assessment of changes promoted by LIRE-BFR on arterial stiffness markers in humans was performed.

Fig 1. Flow diagram of the selection steps in the present systematic review.

3.2 Quality of assessment

The Cochrane Collaboration’s tool for assessing risk could only be used for four studies (19-22), as the other included study did not utilize a randomized design (23). The review authors’ judgements about each risk of bias is shown in Figure 2 as percentages across all included studies and detailed in Figure 3 for each study. Also, all studies analyzed were deemed to be at ‘unclear risk’ of selection bias due to inadequate sequence generation and one study for lack of allocation concealment. Performance bias in the four randomized design studies was ranked as ‘high risk’ as all studies did not use a double-blind design. However, one study followed a single-blinded study design where staff members who performed outcome assessment were blinded – therefore there was a ‘low risk’ of detection these studies.

Fig. 2. Risk of bias summary: review author judgments about each risk of bias item for each included study.

Fig. 3. Risk of bias presented as percentages across all included studies.

3.3 Acute effects of LIRE-BFR on arterial stiffness

The acute studies with LIRE-BFR showed conflicting findings, with some observing positive effects such as reductions in AIx and AP while others indicate negative effects including increases in PWV, cSBP, cDBP and cMAP. A summary of the results is presented in Table 1.

Figueroa et al. (19) demonstrated that 6 sets of 2 different LIRE-BFR leg exercises to failure performed at 40% 1RM with a 10 cm-wide Hokanson device reduced AIx and AP up to 30-minutes post-exercise in young, healthy men and
women. Of note, participants performed a full range of motion while repetition cadence time was slower than in other studies (2-s concentric and 3-s eccentric contraction). Also unique to other included studies in this review, Figueroa et al. (19) utilized intermittent LIRE-BFR application, deflating the cuff pressure during the inter-set and inter-exercise rest intervals.

In contrast, Tai et al. (23) compared the acute effects of post-exercise central hemodynamics between bench press exercise performed at 30% 1RM with LIRE-BFR and high-intensity resistance exercise at 70% 1RM. Their results showed that LIRE-BFR bench press exercise acutely increased AP, AIx and AIx75 parameters in resistance-trained men similarly to high-intensity resistance exercise. Of note, Tai et al. (23) utilized knee wraps and an applied subjective perceived pressure considered moderate ("7/10" on a perceived pressure scale, with "10/10" defined as tight), contrary to other studies that used pneumatic cuffs (Hokanson/KAATSU) to control blood flow restriction.

### 3.4 Longitudinal effects of LIRE-BFR on arterial stiffness

Longitudinal LIRE-BFR studies generally reported neutral effects on markers of arterial stiffness, although one study demonstrated a slight increase in this outcome variable. No studies were longer than 12 weeks duration. A summary of the results is presented in Table 2.

Yasuda et al. (22) showed that LIRE-BFR did not promote changes in arterial stiffness in older adults as evaluated by ABI and CAVI after 12 weeks of training at 20-30% 1RM (5 cm wide KAATSU Master). Moreover, central and peripheral blood pressure measures remained unchanged post-intervention.

Similarly, Clark et al. (21) showed that four weeks of LIRE-BFR leg extension training at 30% 1RM (6 cm wide Hokanson) did not modify PWV and ABI in healthy young adults. In addition, improvements in muscle strength were observed without concurrent modifications in arterial stiffness indicators or other factors associated with adverse hemodynamic or neurodynamic outcomes. In fact, the authors noted increased fibrinolytic activity in the LIRE-BFR group similar to that observed with high-intensity resistance training.

Contrary to the other two studies, Fahs et al. (20) reported that 6 weeks of 2-4 sets of 30% 1RM LIRE-BFR leg extension exercise to failure using a 5 cm wide KAATSU device produced small albeit statistically significant increases (~6.7%) in arterial stiffness assessed by PWV without any changes in venous compliance in middle-aged men and women (40-64 years old). Further, LIRE-BFR did not improve post-occlusive calf blood flow. Of note, this study was a within-subject design, where one leg performed LIRE-BFR and the other performed free-flow exercise leading the authors to speculate that peripheral, not central changes occurred, driving the changes in PWV.

### 4. Discussion

Based on the paucity of data available in humans, the effect of LIRE-BFR on acute and longitudinal (4-12 weeks) measures of central arterial stiffness appears...
to be mixed in a time-dependent and body-regional manner. Acutely, it appears that lower body LIRE-BFR exercise may induce improvements in aortic hemodynamic markers of arterial stiffness in healthy young adults (19) while upper body LIRE-BFR appears to acutely increase aortic hemodynamic markers of arterial stiffness in a similar manner to high-intensity resistance training (HIRT) (23). In studies with a duration of up to 12 weeks, it appears that the application of LIRE-BFR in the upper or lower body does not seem to affect markers of arterial stiffness (21, 22), although this is not a universal finding (20). These conflicting acute and chronic responses may be attributed in part by (i) the type and size of the applied BFR cuff (i.e., narrow elastic vs. wide nylon), (ii) specific BFR application parameters (i.e., continuous vs. intermittent), (iii) whether or not exercise is carried out to volitional failure and (iv) the magnitude of the application pressure (i.e., sub-occlusive or occlusive). These variables contribute significant heterogeneity in methodology and make it challenging to draw any firm conclusions as to the effects of LIRE-BFR on central hemodynamics in different populations and body regions. Based on current evidence, findings lend support to our hypothesis that LIRE-BFR exerts similar effects to traditional strength training on central hemodynamics, although this conclusion must be taken cautiously given the limited research to date.

Increased arterial stiffness is the main age-related risk factor that promotes systolic hypertension (24) and cardiovascular disease (CVD) (25). Pulse wave velocity (PWV) is considered the gold standard, non-invasive technique to assess arterial stiffness in humans (Supp Image 1) (26). Alternative approaches comprise indirect indices of arterial stiffness obtained in the vascular and hemodynamic systems, respectively, including central blood pressure, augmentation pressure (AP), and the augmentation index (Alx). While not providing the sensitivity of PWV, elevations of these indirect markers such as Alx have been proposed to be an independent risk factor for CVD (27).

Carotid-femoral PWV is measured by taking the difference in time delay of pressure waveforms between a proximal, central site (i.e. carotid artery) and a distal, peripheral site (i.e. femoral artery) (Supp Image 1) (26). These measures can be performed synchronously and provide an indication of the compliance (i.e. elasticity) of the aortic arterial supply. As stiffer arteries transmit waveforms at higher velocities compared to more compliant (more elastic) arteries, observed increases in PWV suggest impairments in central arterial compliance (26). Higher PWVs have an immediate impact on aortic hemodynamics by increasing myocardial workload because early return of the reflected wave from the periphery leads to increased central systolic pressure, augmenting left ventricular afterload and reducing coronary perfusion (28). Chronic increases in left ventricular afterload have been associated with adverse cardiac remodeling (i.e. concentric left ventricle hypertrophy) and progression to heart failure (29). Increases in PWV have also been linked to age independent changes in risk factors for atherosclerosis and other risk factors (26, 30), highlighting the need for strategies to mitigate chronic increases in central arterial stiffness.

In this review, we attempted to systematically evaluate the literature in an effort to make evidence-based, practical recommendations as to the acute and chronic effects of LIRE-BFR on arterial stiffness markers. As acute and chronic
changes in central (i.e. aortic) arterial stiffness are often not considered when prescribing LIRE-BFR, it is essential to discuss how LIRE-BFR may impact the central hemodynamic system, especially as its popularity as a therapeutic rehabilitation intervention tool continues to expand (31). Previous reviews have focused on the potential for LIRE-BFR to negatively impact the metaboreflex arm of the exercise pressor reflex in at-risk populations (15, 16), potentially increasing the risk of adverse events both during and following exercise performed with restricted blood flow. Further, only a limited number of studies have examined the acute and chronic effects of LIRE-BFR on markers of central arterial stiffness, highlighting the need for a systematic review on this topic. In order to provide appropriate recommendations for best practice based on the current literature, the effects of LIRE-BFR versus HIRT on acute and chronic markers of arterial stiffness warrant discussion.

Performing concurrent (i.e. alternating cardiovascular and resistance training) exercise has been shown to produce favorable changes in brachial blood pressure and PWV (32) and reduce the risk of adverse cardiovascular events, especially in hypertensive individuals (33). However, some individuals may choose to perform only one mode of exercise (i.e. aerobic or resistance training only). Chronic HIRT (60-70+% 1-RM) has been shown to promote muscular fitness, reduce morbidity (34) and mortality (35), and improve other cardiovascular risk factors (i.e. plasma triglyceride levels and peak VO\textsubscript{2}) in young and old individuals, accompanied by inconsistent reductions in brachial blood pressure in hypertensive populations (36).

Despite the aforementioned long-term and chronic benefits of HIRT, research suggests that acute HIRT can increase intra-exercise systolic and diastolic brachial blood pressure values to reach potentially unsafe levels, especially in older individuals with pre-existing conditions leading them more prone to aneurysms and vascular hemorrhages (37). These peripheral blood pressure changes, while measured empirically at the brachial artery, are also acutely reflected centrally as increases in central hemodynamics (i.e. elevated aSBP, aDBP, aMAP) for up to 30 minutes post-exercise (38). Over time, the hemodynamic responses to HIRT may influence central vascular function due to the imposed demands of the exercise (i.e. high fluctuations in intra-exercise vascular pressures), may therefore lead to increases in aortic stiffness. Indeed, chronic HIRT has been shown to increase measures of central arterial stiffness (39-42), although this appears to be an inconsistent finding based on exercise routine (i.e. upper vs. lower vs. full body) (43, 44), volume of training (43), contraction type (45) and timing of assessment (42).

Therefore, it is important to investigate alternative solutions for individuals who want to obtain the benefits of chronic HIRT but may be unable to engage in such exercise due to musculoskeletal problems, medical complications and/or cardiovascular conditions. LIRE-BFR has been proposed as an alternative to HIRT as it can elicit equivalent benefits on muscle mass and strength using loads as light as 20% of 1RM (6, 39, 46). However, its safety in practice has recently been questioned (15, 16), especially in at-risk populations. This systematic review extends the discussion of safety in LIRE-BFR exercise by reporting on the acute (Table 1) and longitudinal changes (Table 2) in arterial stiffness markers in
a variety of populations (healthy old/young men and women). Collectively, the available data indicated that the use of LI RE-BFR alters central hemodynamic responses of arterial stiffness in a similar time-dependent manner as HIRT despite the use of significantly lighter loads (20-40% 1RM).

To our knowledge, there have been no previous investigations into BFR application strategies to attenuate the acute central hemodynamic responses to LI RE-BFR. To establish such strategies has potential implications for those with pre-existing medical conditions in order to reduce the risk of adverse responses during and following acute protocols of LI RE-BFR (15, 16). Similar to observations in the HIRT literature, studies that showed no effect or a reduction in acute or chronic markers of central arterial stiffness utilized lower body exercise (19, 21, 22), although a single study found that older participants with pre-existing medical conditions exhibited slight increases in pulse wave velocity (PWV) over 6 weeks (20).

Acutely, only two studies met our inclusion criteria (19, 23). Neither study utilized PWV as an outcome measure, instead of using indirect measures (cPP, AP and AIx) to infer central hemodynamic responses. Further, both studies utilized different experimental LI RE-BFR designs, making it challenging to draw any meaningful conclusions. Figueroa et al. (19) utilized single-joint lower body knee extension and knee flexion exercise to failure at 40% 1RM using 100 mm Hg applied pressure in an intermittent application approach with a 10 cm wide nylon cuff. Conversely, Tai et al. (23) employed a multi-joint upper body non-failure bench press exercise at 30% 1RM with a self-selected “7/10” (10 being tight as possible) perceived pressure applied in a continuous manner. The only commonality between the two methodologies is the age of the participants (between 20-30 years old) and the indirect outcome measures used to evaluate central hemodynamics.

Only three studies that investigated longer-term LI RE-BFR met our inclusion criteria (20-22). Two of the three studies (20, 21) utilized PWV whereas one (22) used CAVI and ABI to evaluate changes in central hemodynamics. Of the two studies that utilized PWV, both showed conflicting results likely in part to similar methodological issues described in the prior paragraph. Clark et al. (21) compared central hemodynamic responses between HIRT and LI RE-BFR in young adults over a 4-week study period, with participants performing bilateral knee extension exercise 3 times per week using 3 sets to volitional failure at 30% 1RM. The LI RE-BFR protocol used a 6 cm wide Hokanson nylon cuff set to 130% brachial systolic blood pressure. Alternatively, Fahs et al. (20) conducted a randomized within-subject design in older adults where one leg served as the LI RE-BFR condition and the other served as the LI RE control. Both legs performed between 2-4 sets to volitional fatigue at 30% 1RM using a 5 cm wide KAATSU device between 150-240 mm Hg applied pressure that the authors measured as subocclusive in all participants. Similar to Fahs et al. (20), Yasuda et al. (22) investigated arterial stiffness measures in older adults but excluded those with pre-existing conditions. Their methodology also employed both single-and multi-joint leg non-failure exercise (unique to other studies included in this review) for 12 weeks and showed no adverse responses to arterial stiffness measures. Synthesizing the results of both studies, it appears that the available
evidence suggests negligible or slightly elevated measures of arterial stiffness following a longitudinal 4-12 week lower-body LIRE-BFR in older, but not younger adults. The increases in PWV by Fahs et al. (20) of ~6.7% are consistent with some other studies using HIRT (39-42) but not others (43). Last, due to the within-subject design of Fahs et al. (20), the authors hypothesized that the changes in PWV that did occur were peripheral in origin, likely due to local vascular adaptations. Fahs et al. (20) noted that 9 of the 16 individuals exhibited decreases in arterial stiffness measures in the free-flow group while 7 exhibited increases. Conversely, 14 of the 16 participants in the LIRE-BFR group increased PWV. It is interesting to note that the population included within the study was older adults, some of which had pre-existing conditions. These pre-existing conditions (i.e., hypertension) have a larger capacity to exhibit altered muscle metabo- and mechanoreflexes, heightening the systemic response to LIRE-BFR (15, 16). The lack of consistency between methodologies and protocols – in particular applied LIRE-BFR pressures – make it challenging to compare the responses in arterial stiffness changes between different studies.

The use of personalized pressures, known as limb occlusion pressure (LOP), may provide for a more objective way to understand the various stressors of BFR exercise and mitigate risk of acute adverse events, especially in at-risk populations. LOP accounts for some of the methodological limitations observed in the present review (different cuff widths, limb circumferences and inter-individual differences in blood pressure) and is now the standardization approach recommended in clinical practice and research (47). In this systematic review, only one study explicitly standardized the BFR application pressure using LOP (20) while others used arbitrary pressures (19, 22), practical LIRE-BFR (23) or pressures relative to brachial systolic blood pressure (21).

Another strategy to potentially mitigate changes in central hemodynamics is whether or not the cuff is applied continuously or intermittently through LIRE-BFR. Only one study (19) included in our systematic review utilized an intermittent application approach whereas all other studies had the BFR application on continuously (20-23). Intermittent application involves deflation of the cuffs during the intra-exercise rest period when multiple sets of exercise are performed and may be an alternative approach for individuals with medical risk factors to obtain the benefits of LIRE-BFR exercise without the heightened cardiovascular and hemodynamic responses (48). A single study showed that maintaining cuff pressure during the rest periods significantly increased post-exercise release of noradrenaline as well as brachial measures of blood pressure using a failure-type leg extension LIRE-BFR protocol, although the loads (20% 1RM vs. 40% 1RM) and cuff type (Hokanson vs. KAATSU) were different (49) from those of Figueroa et al. (19). As intra-exercise brachial systolic and diastolic blood pressures are heightened in a continuous application mode compared with the same exercise performed without blood flow restriction (15), intermittent application may be a suitable strategy to reduce cardiovascular and hemodynamic stress (48).

The limited evidence from Figueroa et al. (19) suggests the possibility that acute measures of arterial stiffness – at least during lower-extremity exercise – may be attenuated with inter-set cuff deflation although, more comparative
research on LIRE-BFR applications are needed to make more precise recommendations on this aspect especially when BFR application is standardized using LOP. A recent study showed that intermittent and continuous applications standardized to a relative pressure of 50% LOP provides similar levels of metabolic stress, muscle activation and cellular swelling (50—all factors purported to play a mediating role in the hypertrophic response to exercise with LIRE-BFR. One prior study by Neto et al. (51) showed comparable outcomes over 6 weeks between continuous and intermittent protocols using both multi- and single-joint upper body exercise, although the pressures used were higher (80% LOP) than what is recommended in practice. The only other study besides Neto et al. (51) that could be located resulted in similar muscle mass gains between conditions over 5 weeks despite using arbitrary pressures (52). More research is needed on determining whether or not intermittent BFR application could be a suitable approach to maximizing muscle mass and strength gains while minimizing central hemodynamic stress and subsequent changes in arterial stiffness.

Acute increases in measures of central arterial stiffness following LIRE-BFR may appear deleterious. However, similar to muscle tissue, vascular tissue (i.e. conduit arteries, arterioles etc.) also adapts to imposed stress (53-55). In muscle, unaccustomed LIRE-BFR training may produce myofiber damage (evidenced via increases in venous myoglobin and creatine kinase concentrations) (56) but protects against future damage via the repeated-bout effect (57), whereas vascular tissue responds by vasodilating secondary to reactive hyperemia (53). In LIRE-BFR calf exercise, acute measures of conduit artery vasodilation (measured by flow-mediated dilatation, FMD) have shown to be transiently enhanced (53), likely a byproduct of the mechanical compression from the cuff combined with the elevated hypoxia compared to normal LIRE. Hunt et al. (53) demonstrated a 6-week time-course progression of local vascular adaptation beginning first with acute increases in FMD over the first 4 weeks, followed by an increase in dilatory capacity in week 4, and ending with a return to baseline FMD but an increased maximal conduit artery diameter. Interestingly, Hunt et al. (54) showed that a 4-week LIRE-BFR handgrip intervention did not promote any changes in FMD, despite that resting brachial artery diameter increased post LIRE-BFR training. These differences in peripheral vascular adaptations between upper- and lower body resistance exercise appear to mirror the changes observed in measures of central arterial stiffness following acute- and chronic bouts of HIRT and LIRE-BFR (discussed above). The acute differences observed between upper and lower body exercise on central arterial stiffness during LIRE-BFR likely mirrors HIRT responses because of the similar perceptual demands of exercise, especially when performed to failure (58, 59). This is especially relevant considering that inflating a cuff to 50 mm Hg pressure in the absence of exercise increases adrenergic release (60) and over LIRE alone (8, 61), and increases in growth hormone and cortisol levels approaching HIRT (62), altogether suggesting a heightened sympathetic response. The elevated perceptual demands and the subsequent adrenergic release from LIRE-BFR exercise could provide some explanation as to why LIRE-BFR shares similar central vascular responses as HIRT, although this is speculative and requires further research.
4.1 Limitations

This review is not without limitations. A meta-analysis was not performed due to the high heterogeneity of the included studies in terms of application method (continuous vs. intermittent), device (elastic vs. nylon vs. practical LIRE-BFR), volume (failure vs. non-failure) and demographics (young vs. old). Therefore, the conclusions are based on a synthesis of the general trends observed in the limited data available. However, the current body of literature on HIRT appears to share similar trends of acute elevations in markers of arterial stiffness with limited evidence of slight increases in chronic training (38-44). This observation helps strengthen the position that LIRE-BFR may be considered a highly stressful exercise modality independent of the applied protocol (continuous vs. intermittent; elastic vs. nylon etc.) and caution should be used when applying it in individuals with pre-existing medical conditions. Second, the included studies are of moderate methodological quality based on the Cochrane Analysis performed. In particular two areas – blinding of participants/researchers and blinding of outcome assessments – were weak as most of the studies did not report any attempts to employ blinding procedures during the intervention process, albeit obviously this is difficult to achieve due to the intervention itself. Lastly, there were a paucity of studies that utilized PWV (2/5 studies), highlighting the relatively limited knowledge as to the effects of LIRE-BFR using gold-standard assessment techniques. Future research should include PWV methodology and adherence to a standardized protocol (volume-matched or effort-matched) to allow for stronger conclusions and evidence based practical recommendations.

4.2 Practical Implications

More research on healthy and at-risk populations is needed to make stronger recommendations on the acute and long-term central hemodynamic effects of LIRE-BFR performed with personalized pressures and intermittent application. The current body of literature within this systematic review suggests that these two approaches could be used in practice to attenuate the central hemodynamic response to LIRE-BFR exercise. However, as no studies have incorporated both approaches together in one intervention, future research should determine the acute safety and long-term efficacy (muscle mass, strength etc.) of a combined approach before stronger practical recommendations can be given.

5 Conclusion

In the upper body, it appears that LIRE-BFR acutely augments central blood pressures and pulse wave velocity indicating increased arterial stiffness in healthy young individuals (23), whereas it does not appear to produce any significant negative post-exercise increases in arterial stiffness following lower body training at least up to 30 minutes post-exercise (19).

Up to 12 weeks, the included LIRE-BFR studies showed no changes in measures of arterial stiffness in healthy young and older people (21, 22). However, a single study reported a small increase in pulse wave velocity following LIRE-BFR training in middle-aged adults (20), warranting caution in individuals...
with pre-existing central hemodynamic risk factors. Hence, LIRE-BFR should be prescribed with caution to avoid unintended adverse responses on arterial stiffness, particularly in older populations with pre-existing medical conditions.

Conflicts of interest

SA is a researcher representative of KAATSU GLOBAL company in Brazil and NR has been previously compensated to speak about LIRE-BFR by MadUp Training, a company that manufactures BFR technology. Otherwise, the authors declare no other conflicts of interest regarding the publication of this manuscript.

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References


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<td></td>
<td>Age: 20-30 years</td>
<td>Exercises: Knee extension and knee flexion, Intensity: 40%1RM</td>
<td>AIx (%) Baseline: 10</td>
<td>AP (mmHg) Rest: 7.1±2.3, Recovery: 4.2±5.1 #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pressures used: 100 mmHg, Device used: E20 Hokanson, Occlusion time: Not reported</td>
<td>cPP (mmHg) - Baseline: 13</td>
<td>cPP (mmHg) Rest: 4.1±3.5, Recovery: 4.3±5.2 #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean and SD was reported</td>
<td>LIRE-BFR</td>
<td>Ax (%): Baseline 4.1±1.0, Recovery 3.1±2.0 #</td>
</tr>
<tr>
<td>Tai et al. (2018)</td>
<td>Non-randomized crossover design</td>
<td>Total duration: 1 session, Exercises: Bench press, Intensity: 30%1RM</td>
<td>AP, AIx</td>
<td>Both groups changed indirect markers of arterial stiffness after session</td>
</tr>
<tr>
<td></td>
<td>n= 16M</td>
<td>Groups: LIRE-BFR, HL and Control, Occlusion time: Not reported</td>
<td>cPP (mmHg) Rest: 41</td>
<td>cPP (mmHg) Rest: 39±6.5, Recovery: 46.5±7.0 #</td>
</tr>
<tr>
<td></td>
<td>Age: 20-30 years</td>
<td>Exercises: Bench press, Intensity: 30%1RM</td>
<td>AP (mmHg) Rest: 4.0±2.3</td>
<td>AP (mmHg) Rest: 5.2±3.9, Recovery: 9.6±3.7 #</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occlusion time: Not reported</td>
<td>Pressures used: 100 mmHg, Device used: Knee wraps, Occlusion time: Not reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean and SD was reported</td>
<td>AP (mmHg) Rest: 5.2±3.9, Recovery: 4.1±3.5</td>
<td>AP (mmHg) Rest: 7.1±2.3, Recovery: 4.2±5.1 #</td>
</tr>
</tbody>
</table>

Table 1: The effects of acute studies with blood flow restriction exercise on arterial stiffness in humans

- **Study design and population**
- **Description of intervention**
- **Outcome measures**
- **Main findings (Summary of changes)**
Abbreviations: HL: High load; RPP: rating of perceived pressure; cSBP: central systolic blood pressure; cDBP: central diastolic blood pressure; cMAP: central mean arterial pressure; AIx: augmentation index; AP: augmentation pressure; PWV: pulse wave velocity; 1RM: one repetition maximum. *P<0.05 vs baseline. #P<0.001 vs control.
### Table 2: The effects of longitudinal studies with blood flow restriction exercise on arterial stiffness in humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design and population</th>
<th>Description of intervention</th>
<th>Outcome measures</th>
<th>Main findings (Summary of changes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clark et al. (2011)</strong></td>
<td>Randomized design</td>
<td>Total duration: 4 weeks - 3 times a week</td>
<td>Pulse wave velocity (PWV)</td>
<td>LIRE-BFR did not alter vascular markers in healthy individuals</td>
</tr>
<tr>
<td>n=16 (14M, 2W)</td>
<td>n=16 (14M, 2W)</td>
<td>Exercises: BIL KE</td>
<td>Ankle-Brachial index (ABI)</td>
<td>Mean and SD was reported</td>
</tr>
<tr>
<td>Groups: HL and LIRE-BFR</td>
<td>Groups: HL and LIRE-BFR</td>
<td>Intensity: 30%1RM</td>
<td></td>
<td>LIRE-BFR</td>
</tr>
<tr>
<td>Age: 24±1 years</td>
<td>Age: 24±1 years</td>
<td>Protocol: 3 sets until volitional failure</td>
<td>PWV (m/s)</td>
<td>(Pre: 9.26 ± 0.39 / Post: 8.73 ± 0.32)</td>
</tr>
<tr>
<td></td>
<td>w ith 90s rest interval be tween sets</td>
<td>Pressures used: 130% bSBP</td>
<td>ABI (unit)</td>
<td>(Pre: 1.15 ± 0.03 / Post: 1.09 ± 0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Device used: Hokanson</td>
<td></td>
<td>HL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occlusion time: Not reported</td>
<td>PWV (m/s)</td>
<td>(Pre: 8.19 ± 0.27 / Post: 7.94 ± 0.40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ABI (unit)</td>
<td>(Pre: 1.08 ± 0.04/ Post: 1.07 ± 0.04)</td>
</tr>
<tr>
<td><strong>Fahs et al. (2013)</strong></td>
<td>Randomized design</td>
<td>Total duration: 6 weeks – 3 times a week</td>
<td>Pulse wave velocity (PWV)</td>
<td>LIRE-BFR promotes small increases in peripheral arterial stiffness</td>
</tr>
<tr>
<td>n=16 (5W, 11M)</td>
<td>n=16 (5W, 11M)</td>
<td>Exercises: UNI KE</td>
<td></td>
<td>Mean and SD was reported</td>
</tr>
<tr>
<td>Groups: LIRE-BFR limb, Control limb</td>
<td>Groups: LIRE-BFR limb, Control limb</td>
<td>Intensity: 30%1RM</td>
<td></td>
<td>LIRE-BFR limb (PWV (m/s) – Pre: 8.9 (0.8) / Post: 9.5 (0.9) *</td>
</tr>
<tr>
<td>Age: M (55 ± 8 years), W (57 ± 5 years)</td>
<td>Age: M (55 ± 8 years), W (57 ± 5 years)</td>
<td>Protocol: 2-4 sets to volitional failure</td>
<td></td>
<td>Control limb (PWV (m/s) – Pre: 9.0 (1.2)/ Post: 9.0 (1.1)</td>
</tr>
<tr>
<td></td>
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<td>w ith 60s rest interval be tween sets</td>
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<td></td>
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<td>Pressures used: 150-240 mm Hg</td>
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<td></td>
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<td>Device used: KAATSU Master Mini</td>
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<td></td>
<td></td>
<td>Occlusion time: Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yasuda et al.</strong></td>
<td>Randomized design</td>
<td>Total duration: 12 weeks – 2 times a week</td>
<td>Cardio ankle vascular index (CAVI)</td>
<td>LIRE-BFR did not affect arterial stiffness in healthy older people</td>
</tr>
</tbody>
</table>
Groups: LIRE-BFR (n=9), Non-exercise control (n=10)

Exercises: BIL KE and LP

Intensity: 20-30% 1RM

Protocol: 4 sets of 30, 20, 15, 10 repetitions

Age: 61-84 years old

with 30s rest interval between sets

Pressures used: 120-270 mm Hg

Device used: KAATSU Master

Occlusion time: 11 minutes

Abbreviations: HL: High load; 1RM: one repetition maximum; SD: Standard deviation; bSBP: Brachial systolic blood pressure; KE: Knee extension; LP: Leg press; BIL: Bilateral; UNI: unilateral. *p < 0.05 time effect.