Low Intensity Resistance Exercise Training with Blood Flow Restriction: Insight into Cardiovascular Function, and Skeletal Muscle Hypertrophy in Humans

Song-Young Park¹,², Yi Sub Kwak³, Andrew Harveson², Joshua C Weavil¹,², and Kook E. Seo⁴

¹Geriatric Research, Education, and Clinical Center, George E. Whalen VA Medical Center, Salt Lake City 84148, USA, ²Department of Exercise and Sport Science, University of Utah, Salt Lake City 84148, USA, ³Department of Physical Education, Dong-Eui University, Busan 614-714, Korea, ⁴Department of Sports Science, Pusan National University, Busan 609-735, Korea

INTRODUCTION

The loss of muscle strength and mass with age, also known as sarcopenia, is a common detrimental issue leading to a decline in functional capacity, mobility, and endurance in the elderly [1-3]. In addition to sarcopenia, cardiovascular disease (CVD) is also a common disease that results from decreased cardiac and vascular smooth muscle elasticity in the elderly [4]. Also, advancing age may cause a reduction in central arterial compliance, which is highly related to endothelial dysfunction [5-7]. However, age-related arterial stiffening and endothelial dysfunction may be restored by lifestyle modifications such as regular exercise training [8-10].

Previously, several studies have reported a reduction in arterial stiffness following an 8-week course of aerobic exercise [11]. These exercises should target major muscle groups 2-3 d · wk⁻¹ at a training intensity of more than 65% of the subject’s one-repetition maximum [13]. However, the elderly and individuals who have chronic diseases may find it difficult to perform regular exercise at moderate to high intensities. Although the beneficial effects of resistance exercise on skeletal muscle function have been well documented, the increase in blood pressure during resistance exercise in older adults who have high blood pressure and other forms of CVD are still problematic. In addition, some studies have reported that chronic resistance exercise training (RET) may increase central and peripheral arterial stiffness and sympathetic activity [14-17]. Therefore, it is imperative to...
propose an alternative training protocol aimed at increasing muscular strength and mass, but without the detrimental effects on cardiovascular function in older adults. Recently, blood flow restriction (BFR) combined with low intensity resistance exercise (LIRE) has been suggested as a useful exercise protocol to gain muscular strength and mass without an increase in blood pressure. BFR+LIRE is typically performed by placing a narrow compressive cuff around an appendicular limb and inflating it immediately prior to exercise. The pressure of the cuff is around super systolic (150–350 mmHg), and the exercise intensity is 25–45% of maximum voluntary contraction (MVC). BFR+LIRE may be used for a variety of exercise modalities including both isometric and isotonic contractions including chest press, arm curl, leg extension, squat, etc. Improvements in both isometric and isotonic contractions including chest press, arm curl, leg extension, squat, etc. Improvements in muscular strength and mass in older people have been reported in many studies utilizing BFR+LIRE [18-26]. Moreover, several studies reported that BFR+LIRE training acutely reduced arterial stiffness along with improving muscular strength [8,27]. The primary benefit of using BFR+LIRE is that it improves muscular strength and cardiovascular function concurrently. Additionally, it is suitable for special populations such as the elderly and diseased populations who cannot perform traditional resistance or aerobic exercise training [28]. This review will mainly highlight the impact of BFR+LIRE, first on skeletal muscle hypertrophy, including hormonal and transcriptional factors, and second on vascular function including endothelial function and cardiovascular autonomic modulation. 

**IMPACT OF BFR+LIRE ON HORMONAL FACTORS ASSOCIATED WITH MUSCLE HYPERTROPHY**

Muscle hypertrophy and increased strength following single high-intensity resistance exercise bouts are generally thought to be associated with the recruitment of high threshold motor units [29,30]. Recruitment of these motor units results in an increase in mechanical stress [31,32], endocrine responses [33], and metabolite accumulation [34]. For example, large, acute increases in growth hormone (GH) immediately after exercise has been theorized to stimulate the secretion of insulin like growth factors (IGFs) leading to increased protein synthesis and ultimately muscle hypertrophy [35]. To this point, BFR+LIRE has been popularized for nearly a decade because of its ability to augment endocrine response [43]. The impact of BFR+LIRE after a single bout of resistance exercise in human skeletal muscle [47-49]. Indeed, this rapid time course allows for the acute evaluation of the hypertrophic potential of BFR+LIRE. Recently, Fujita and Yasuda reported that muscle protein synthesis and ribosomal S6 kinase (S6K) phosphorylation are increased after a single bout of BFR+LIRE [50]. These acute changes in transcriptional factors associated with muscle hypertrophy after BFR+LIRE may be explained by the up-regulation of hypertrophy-associated genes including phosphoinositide 3-kinase (PI3K), protein kinase B (AKT), and mTOR. Drummond et al. demonstrated that the short duration of hypoxia and reperfusion induced by BFR promotes cell survival and cell growth adaptations within skeletal muscle by the activation of the mTOR pathway [46]. In addition, up-regulation of vascular endothelial growth factor (VEGF), considered an important modulator in vascularlogenesis and angiogenesis, is essential for hypertrophy and can be stimulated by hypoxia and lactate accumulation [46,51-53]. Moreover, an increase in the rate of angiogenesis has been described when lactate levels are elevated, thus eliciting a greater hypertrophic stimulus [54]. According to such findings, lactate accumulation derived from BFR-induced hypoxia is a potent stimulus for muscle hypertrophy. Taken together, the above referred studies points towards the conclusion that BFR+LIRE appears to be an effective method for inducing an increase in hypertrophy related transcriptional factors in skeletal muscle via induction of hypoxia compared to resistance exercise without BFR. 

**IMPACT OF BFR+LIRE ON CHANGES IN HEMODYNAMICS**

The impact of BFR with RT on hemodynamic parameters is well documented. Previously, studies suggested that moderate to heavy resistance exercise involving large muscle groups, especially those utilizing isometric contractions, evoke
a significant increase in mean arterial pressure as both sys-
tolic and diastolic pressure are elevated [55,56]. Furthermore,
when compared with younger counterparts, older individuals
exhibit a similar or even greater pressor response to iso-
metric exercise [57,58]. As the intensity of the resistance
exercise is increased, there are concurrent increases in blood
pressure, which significantly increase pulse pressure ampli-
fication estimated by the elevation of aortic pulse wave ve-
locity (a surrogate of aortic stiffness) in humans [14,59,60].
These findings highlight the influence of exercise intensity
on the biophysical and elastic properties of the heart’s large
central arteries and the possible relationship of exercise in-
tensity on the cardiovascular risk of a patient with in-
creased CVD risk factors [61].

While the exercise-induced pressor response is considered
inherent to resistance exercise, it is important to note that
BFR can elicit significantly greater changes in blood pres-
sure as compared to traditional exercise [62]. Renzi, et al.
cautioned the prescription of BFR for those with compro-
mised cardiovascular systems such as the elderly and those
with CVD. Their findings demonstrated an exaggerated heart
rate response (cardiac reactivity) to BFR over non-BFR, de-
spite a similar cardiac output in young, healthy adults [62].
This led to significantly greater cardiac work and myocardial
oxygen demand after BFR+ walk training [63]. However,
contradicting results have been shown in elite athletes, as
BFR positively impacted stroke volume [64].

Due to the robust changes in blood flow dynamics during
BFR, it is important to understand the peripheral and cen-
tral blood flow changes that take place and how these changes
may impact the safety of BFR. In this regard, Takano et al.
demonstrated a similar response in BFR as compared to a work-matched non-BFR control in total peripheral re-
sistance and ankle brachial index [65]. Blood flow changes
post-exercise have demonstrated varying results following
isometric exercise, with both increases [66] and decreases
[67] being reported. Post exercise blood flow has also been
found to be increased to a larger extent following chronic
BFR as compared to traditional resistance exercise [68]. The
authors suggested that the increase in post exercise blood
flow may be due to increased venous compliance, which en-
able increased arterial inflow post exercise [68]. Additional
explanations have pointed to oxygen restriction and vaso-
active metabolite accumulation (e.g. H+, CO2, lactate, etc.)
as precursors to post exercise blood flow [69].

In sum, the peripheral blood flow response following BFR+exer-
cise appears to be similar to that of regular exercise
and should not be a cause for concern regarding the safety
of this training modality.

**IMPACT OF BFR+LIRE ON ENDOTHELIAL
FUNCTION**

Although the impact of BFR+LIRE on vascular function
has not been well documented, BFR+LIRE does not appear
to negatively affect blood vessel function as determined by
the arterial compliance of large and small arteries [27,70].
Walk training with BFR has also been shown to induce pos-
itive effects on both muscle hypertrophy and carotid arte-
rial compliance, concurrently [23]. In contrast, a study sug-
gested that flow-mediated vasodilatation, an indicator of en-
dotheilial function, decreased following BFR+walk training.
This decreased endothelial function was explained by ische-
mia-reperfusion injury [62]. Also, Credeur et al. suggested
that 12 weeks of BFR+handgrip exercise training impaired
endothelial function in brachial arteries [71]. The authors
explained the functional impairment by the stimulation of
endothelin I, induced by BFR, which increased retrograde
flow in working muscle [71]. Although endothelial function
in the vasculature is important for understanding the mech-
nisms of alterations in function following BFR+LIRE, there
are limited studies and inconsistent results investigating
this phenomenon. Therefore, further studies are warranted
to understand how BFR+LIRE affects vascular function.

**LIMITATIONS OF BFR+LIRE AND FUTURE
DIRECTIONS**

There is lack of standardized exercise prescription for BFR
exercise, including pressure, exercise duration, and intensity.
In general, BFR studies inflate pressure cuffs’ pressures to
a value higher than brachial diastolic blood pressure (cuff
pressure of 100–200 mmHg) in order to restrict venous blood
flow [21,67,79]. Cuff pressure is also inflated higher than
brachial systolic blood pressure (cuff pressure of ≥ 300 mmHg)
to stimulate a restriction in arterial blood flow [38,80,81] with
20–45% of MVC. However, there are no standardized cuff
pressures or exercise intensities in the BFR+LIRE studies,
which results in varied outcomes. Cook et al. suggested that continuous venous BFR (BFR during whole exercise session) with 20% of MVC is the most demanding and potent stimulator for muscle growth [82]. Initially, Fales and colleagues investigated the different effects between venous BFR using low cuff pressure, and complete arterial BFR using a continuous venous BFR (BFR during whole exercise session). This certainly warrants further investigation. Furthermore, the safety of BFR+LIRE training has not been established in diseased populations. Even with these unsolved issues, many studies confirm that BFR+LIRE training improves muscular strength and mass more efficiently (i.e. lower exercise intensity) compared to exercise without BFR. Thus, BFR+LIRE training is not only a useful method for improving or maintaining the age-associated decreases in functional capacity but also an efficient exercise modality for rehabilitation by promoting positive changes in muscle while only requiring low intensity exercise in humans.

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