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Blood flow restriction training and the exercise pressor reflex: a call for concern

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Spranger MD, Krishnan AC, Levy PD, O’Leary DS, Smith SA. Blood flow restriction training and the exercise pressor reflex: a call for concern. Am J Physiol Heart Circ Physiol 309: H1440–H1452, 2015. First published September 4, 2015, doi:10.1152/ajpheart.00208.2015.—Blood flow restriction (BFR) training (also known as Kaatsu training) is an increasingly common practice employed during resistance exercise by athletes attempting to enhance skeletal muscle mass and strength. During BFR training, blood flow to the exercising muscle is mechanically restricted by placing flexible pressurizing cuffs around the active limb proximal to the working muscle. This maneuver results in the accumulation of metabolites (e.g., protons and lactic acid) in the muscle interstitium that increase muscle force and promote muscle growth. Therefore, the premise of BFR training is to simulate and receive the benefits of high-intensity resistance exercise while merely performing low-intensity resistance exercise. This technique has also been purported to provide health benefits to the elderly, individuals recovering from joint injuries, and patients undergoing cardiac rehabilitation. Since the seminal work of Alam and Smirk in the 1930s, it has been well established that reductions in blood flow to exercising muscle engage the exercise pressor reflex (EPR), a reflex that significantly contributes to the autonomic cardiovascular response to exercise. However, the EPR and its likely contribution to the BFR-mediated cardiovascular response to exercise is glaringly missing from the scientific literature. Inasmuch as the EPR has been shown to generate exaggerated increases in sympathetic nerve activity in disease states such as hypertension (HTN), heart failure (HF), and peripheral artery disease (PAD), concerns are raised that BFR training can be used safely for the rehabilitation of patients with cardiovascular disease, as has been suggested. Abnormal BFR-induced and EPR-mediated cardiovascular complications generated during exercise could precipitate adverse cardiovascular or cerebrovascular events (e.g., cardiac arrhythmia, myocardial infarction, stroke and sudden cardiac death). Moreover, although altered EPR function in HTN, HF, and PAD underlies our concern for the widespread implementation of BFR, use of this training mechanism may also have negative consequences in the absence of disease. That is, even normal, healthy individuals performing resistance training exercise with BFR are potentially at increased risk for deleterious cardiovascular events. This review provides a brief yet detailed overview of the mechanisms underlying the autonomic cardiovascular response to exercise with BFR. A more complete understanding of the consequences of BFR training is needed before this technique is passively explored by the layman athlete or prescribed by a health care professional.

muscle metaboreflex; muscle mechanoreflex; Kaatsu training; occlusion training; hypertension; heart failure; peripheral artery disease

BLOOD FLOW RESTRICTION (BFR) training is an exercise practice developed to increase skeletal muscle mass and strength in normal, healthy individuals (1, 27, 102, 129, 135, 144, 166, 188, 210, 211, 214). Additional beneficial effects on postocclusive blood flow (144) and microvascular filtration capacity (39), perhaps mediated by vascular endothelial growth factor (58, 64, 187), have been reported as well. These effects may further contribute to performance improvements through enhancement of aerobic capacity and endurance by promoting angiogenesis. Moreover, BFR training is purported to provide health benefits to the elderly (2, 62, 67, 195, 215), as well as individuals afflicted by certain disease states (e.g., cardiovas-
BLOOD FLOW RESTRICTION TRAINING AND THE EXERCISE PRESSOR REFLEX

Physiological Adaptations to Exercise Training

Within skeletal muscle, a mismatch between oxygen delivery and oxygen demand occurs during high-intensity exercise. The increase in oxygen demand by skeletal myocytes is met via increased muscle blood flow, which can reach upward of 80% of total cardiac output (CO) during rigorous dynamic exercise of a large muscle mass (165). A substantial redistribution of this elevated CO also occurs as a result of metabolic vasodilation within the active muscle (active hyperemia) as well as sympathetically mediated vasoconstriction in peripheral vascular beds not essential to the performance of exercise (e.g., splanchnic circulation, kidneys, and inactive muscle) (164). Notwithstanding the rise in skeletal muscle blood flow, production of skeletal muscle metabolites (e.g., protons and lactic acid) that increase muscle force and promote muscle growth (77, 78, 110, 151, 187, 188, 190, 213, 215). Therefore, the fundamental objective of BFR training is to simulate and receive the benefits of high-intensity resistance exercise while merely performing low-intensity resistance exercise.

The Exercise Pressor Reflex

What is categorically missing from the literature regarding Kaatsu training (94, 166) is the likely role played by the skeletal muscle exercise pressor reflex (EPR) in determining the cardiovascular response to physical activity during BFR. The EPR has two functional components, the muscle metaboreflex and muscle mechanoreflex (19, 114, 124). Engagement of these components during exercise is mediated via activation of chemically and mechanically sensitive receptors within skeletal muscle (71). Chemical stimuli [e.g., protons (20, 197), lactic acid (35, 79, 155, 170, 175), potassium (105), diprotonated phosphate (20, 174), and ATP (57, 88, 182)] largely activate group IV afferent nerve fibers predominately associated with the metaboreflex (73, 117). Mechanical stimuli (e.g., pressure and stretch) primarily activate group III sensory neurons largely associated with the mechanoreflex (76) [although many afferents of both types are poly-modal (72, 79, 156)]. Along with input from central command (a feedforward neural signal originating in the cerebral cortex) and the arterial baroreflex (a feedback neural signal emanating from the carotid sinus and aortic arch), the EPR mediates autonomic adjustments to the cardiovascular system by enhancing sympathetic output while simultaneously reducing parasympathetic activity when engaged during physical activity (Fig. 1) (111, 112, 196, 200). During dynamic exercise, EPR-induced increases in sympathetic outflow generate moderate elevations in mean arterial pressure (MAP) (5, 8, 12, 13, 18, 24, 32, 42, 45, 158, 159, 180). At submaximal intensities, the increase in MAP is principally driven by augmentations in cardiac output (CO) with little or no change in peripheral vascular resistance (18, 31–33, 145, 158, 172, 180, 198). The rise in CO is driven by marked tachycardia (6, 32, 43, 60, 138, 162, 208) coupled with sustained increases in stroke volume (32, 61, 163, 172, 208) supported via enhanced ventricular contractility (dP/dt\text{max}) (25,
31, 61, 139, 180) and central blood volume mobilization (169). As the ability to further elevate CO becomes limited with more strenuous exercise, the rise in MAP is primarily driven by restricting the reduction in total peripheral resistance (14). During static exercise, the EPR likewise evokes considerable elevations in sympathetic activity (123). However, the MAP increases elicited at comparable levels of physical activity (e.g., mild, moderate, and high) are considerably larger during static compared with dynamic exercise (122, 123, 157). This is primarily due to the fact that peripheral vascular resistance is either unchanged or slightly increased during static exercise in part attributable to the compressive effects of increased muscle tissue pressure. Upon this background, sympathetically mediated increases in CO produce marked elevations in blood pressure.

Clearly the EPR plays an essential role in regulating the cardiovascular system during both dynamic and static exercise. Moreover, the EPR is likely engaged during BFR training maneuvers. For example, Loenneke et al. (100) reported that wider BFR cuffs (13.5 cm) restrict arterial blood flow at a lower cuff pressure than narrower BFR cuffs (5.0 cm). It can be reasoned from these findings that, for a given cuff pressure, wider cuffs result in a greater reduction in blood flow than narrower cuffs. Importantly, Rossow et al. (153) reported substantially greater pressor responses in individuals performing dynamic knee extension exercise with wider BFR cuffs (13.5 cm) inflated around their upper thighs compared with narrower BFR cuffs (5.0 cm). These data support the contention that the mechanical restriction of blood flow to the exercising muscle during BFR exercise activates the EPR and can do so in a graded fashion dependent on cuff width. Therefore, it is critically important to fully appreciate the physiological conditions under which the components of the EPR (metaboreflex and mechanoreflex) are stimulated, especially so in individuals with cardiovascular diseases such as hypertension (HTN), heart failure (HF), and peripheral artery disease (PAD).

The Muscle Metaboreflex in Health and Cardiovascular Disease

The muscle metaboreflex is an extraordinarily powerful cardiovascular reflex only rivaled by the cerebral ischemia reflex in terms of its capacity to raise arterial blood pressure (160). Wyss et al. (208) demonstrated using conscious, chronically instrumented dogs trained to run on a treadmill in which during mild exercise substantial reductions in skeletal muscle
blood flow were required before metabolites accumulated sufficiently to activate the metaboreflex. Thus muscle is normally well perfused, and a wide margin for “flow error” exists. In HF, skeletal muscle blood flow is significantly lower at rest and during exercise (10, 26, 140). Therefore, the metaboreflex is engaged at lower workloads, as the flow is lower and much closer to the trigger or threshold level for the reflex. As workload rises, the normal level of flow becomes closer to this threshold level such that even in normal subjects little or no room for a flow error exists, and the reflex likely becomes tonically engaged at moderate work rates. Alternatively, other evidence suggests that it is not a decrease in flow per se that triggers the accumulation of muscle metabolites but rather the reduction in oxygen delivery to the muscle (170). In any event, the prevailing consensus is that the muscle metaboreflex is not engaged until moderate to severe dynamic exercise is achieved, exercise intensities known to produce high levels of metabolites with sufficient time for accumulation (14, 141, 158, 208). However, there is evidence in humans (7) and animals (3) suggesting that the reflex may likewise be activated during mild dynamic exercise. During static exercise, the reflex is engaged much more quickly because of the relatively large increases in intramuscular pressure characteristic of isometric contractions (122, 157). Blood flow to the muscle is immediately compromised as the result of physical compression of vascular tissue, leading to the rapid production and accumulation of metabolites (122, 157). As evidence, excitatory impulses from chemically sensitive group IV afferents have been recorded in cats as early as 5–20 s after the onset of contraction, directly in proportion to the intensity of exercise (72). As with dynamic exercise, the most robust increases in blood pressure occur at moderate to severe intensity levels although modest elevations can be evoked during mild static contractions. Importantly, the muscle metaboreflex may indeed be activated more vigorously even at lower intensities of dynamic and static exercise in disease states in which perfusion to skeletal muscle is impaired [e.g., HTN (53, 85, 127), HF (30, 55, 178), and PAD (89, 101, 130, 192)].

Our laboratories have extensively investigated the function of the muscle metaboreflex during exercise in normal and disease states such as HTN and HF. Resting sympathetic nerve activity (SNA) is heightened in HF (17, 23, 55, 56, 82, 87, 136) and HTN (9, 51, 54, 65, 109, 113, 125, 194). During submaximal dynamic and static exercise, metaboreflex-induced increases in sympathetic outflow are exaggerated in both disease states (26, 36, 55, 56, 127, 137, 173, 181). The Smith laboratory has demonstrated in rats (126, 127), and other laboratories have demonstrated in humans (36, 53), that these accentuated elevations in SNA lead to exaggerated MAP responses to exercise. The O’Leary laboratory has reported attenuated responses in CO, HR, and dP/dt max with muscle metaboreflex activation in dogs with HTN (162) and HF (10, 26, 140). The underlying mechanism mediating these impairments in chronotropic and inotropic function is exaggerated sympathetically mediated coronary vasoconstriction, which restrains coronary perfusion and oxygen delivery to the heart. As evidence in HF, Ansorge et al. (10) reported that, during submaximal dynamic exercise, the ability to raise CO is virtually abolished, the rise in coronary blood flow is restrained, and frank coronary vasocostriction occurs with metaboreflex activation (see Fig. 2). Accentuated coronary constriction tone during exercise may lead to coronary vasospasms, ischemia, arrhythmias, myocardial infarction, or even sudden cardiac death. Recently, Spranger et al. (181) published preliminary data demonstrating a similar phenomenon in HTN.

In addition to HF and HTN, exaggerated metaboreflex-induced cardiovascular responses (e.g., SNA, MAP, and HR) have also been demonstrated in humans with PAD (15, 16, 101) and in a rat model (femoral arterial ligation) employed to study human PAD (86, 89, 91, 103, 183, 192, 193, 209). Clearly, metaboreflex-mediated responses are altered in HTN, HF, and PAD, and the common denominator appears to be the...

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**Fig. 2. Cardiac responses to metaboreflex activation in healthy and heart failure dogs. CO, coronary blood flow (CBF), and coronary vascular conductance (CVC) in response to graded reductions in hindlimb blood flow (HLBF) during mild exercise (3.2 kph) before (left) and after induction of heart failure (right). In normal animals when HLBF is reduced sufficiently, there are large reflex increases in CO and CBF; however, no coronary vasodilation occurs, as indicated by the constant CVC. As a result, all of the increase in CBF occurs via a reflex-induced elevation in arterial pressure (not shown). In heart failure, the ability to raise CO is virtually abolished, the rise in CBF is restrained, and frank coronary vasoconstriction occurs with metaboreflex activation. *P < 0.05 vs. free-flow exercise (without arterial occlusion). NS, no significant change from normal exercise levels. Reproduced with permission from Ansorge et al. (10).**
generation of sympathetic overactivity. As such, individuals with these cardiovascular diseases share the same potential cardiovascular risks during exercise.

The Muscle Mechanoreflex in Health and Cardiovascular Disease

The muscle mechanoreflex likewise contributes significantly to the autonomic cardiovascular response to both dynamic and static exercise. Mechanoreceptors and their associated group III afferent fibers are activated primarily by the mechanical distortion of their receptive fields, a consequence of tissue compression during skeletal muscle contraction (76). As such, mechanosensory neurons are activated rapidly (within 2–5 s in cats) at the onset of muscle contraction in direct proportion to the intensity of the exercise (3, 72). This reflex has been shown to increase sympathetic activity and subsequently blood pressure, even during low-level exercise in rats (128, 176). Germaine to BFR training, it has been reported on several occasions in cats that mechanoreceptors become more sensitive in the presence of metabolites, especially under conditions of limited muscle perfusion (4, 73). Sensitization of the reflex under such conditions enhances its sympathetically mediated cardiovascular response. Because of this fact, evidence in rats suggests that the mechanoreflex is overactivated in disease states in which skeletal muscle perfusion is reduced during exercise (178, 201).

In both HF and HTN, it has been reported that the mechanoreflex contributes significantly to the potentiated sympathetic and pressor responses to physical activity characteristic of each disease (121, 126, 128, 178, 201). With regard to HF, it has been demonstrated on several occasions in both cardiomyopathic animals and patients with HF that mechanoreflex function is abnormally accentuated (121, 177, 178, 201). For example, in rats with dilated cardiomyopathy, passively stretching skeletal muscle (a stimulus designed to preferentially activate the mechanoreflex) has been shown to elicit exaggerated increases in SNA and MAP (177, 178, 201). Furthermore, pharmacologically blocking mechanoreceptors during muscle contraction reduces the evoked cardiovascular response to a greater degree in HF animals compared with healthy controls (178). Accumulating evidence suggests that this heightened mechanoreflex responsiveness results from sensitization of mechanoreceptors by exercise-induced metabolites, metabolites whose removal is compromised because of impairments in muscle perfusion (47, 80, 120). Similar findings have been reported in various animal models of HTN, including the spontaneously hypertensive rat (Fig. 3) and prenatally programmed hypertensive rat (a model of human maternal dietary protein deprivation-induced HTN) (126, 128). In both disease states, these exaggerated sympathetically mediated cardiovascular responses to mechanoreflex activation can be dangerous, increasing the risk for occurrence of a deleterious cardiovascular or cerebrovascular event (147, 149).

BFR Training and Cardiovascular Disease

The altered functions of the metaboreflex and mechanoreflex with the advent of cardiovascular disease must be taken under advisement when considering the implementation of BFR training. With regard to HTN, an alarming one in every three Americans suffers from this malady, and recent data suggest that the ceiling has not yet been reached (49). Moreover, one in every five Americans has undiagnosed and/or untreated HTN (49). To the best of our knowledge, there are no hard statistics on the incidence of HTN in the population of bodybuilding athletes that commonly use BFR training. However, with the heavy use of cardioaccelerants (e.g., caffeine), sympathomimetics (e.g., ephedra alkaloid-containing products), and performance-enhancing drugs among individuals in this population, it is likely that the incidence of HTN is higher than the national average (37). What is more concerning is the percentage of these individuals that may be unaware that they have HTN. Although one of the most effective treatment modalities for HTN is exercise, exercising in HTN can be potentially dangerous (179). Indeed, the American College of Cardiology/American Heart Association 2002 Guideline Update for Exercise Testing warns that individuals with HTN may experience exercise-induced ST segment depression despite no evidence of atherosclerosis (48). Although BFR resistance training is performed during low-intensity exercise, muscle perfusion is mechanically attenuated, and therefore both the muscle mechanoreflex and metaboreflex are likely engaged. Given the dysfunction of each of these reflexes in HTN, individuals performing BFR resistance training with this disease may exhibit exaggerated increases in SNA, which can generate abnormal
elevations in MAP and coronary vasomotor tone. These abnormal responses to exercise could precipitate adverse cardiovascular events.

That being stated, Araujo et al. (11) recently reported that low-intensity BFR strength training in hypertensive women was more effective at reducing postexercise systolic blood pressure than moderate-intensity strength training without BFR. They concluded that low-intensity BFR exercise may be a useful method for reducing blood pressure in individuals with HTN. Similarly, investigating the postexercise hypotensive effects of BFR exercise, Neto et al. (134) recommended that physical education professionals employ low-intensity exercise with BFR as a nonpharmacological intervention for controlling blood pressure in hypertensive patients. Alarmingly, however, additional data from the study by Araujo et al. (11) showed that systolic blood pressure and HR values were markedly higher during BFR exercise compared with exercise without BFR. For example, during the second set of a three-set protocol of knee-extension exercise, systolic blood pressure reached 147 ± 10 mmHg during moderate-intensity exercise without BFR and 183 ± 10 mmHg during low-intensity exercise with BFR. Clearly, there is potential for BFR training to serve as a beneficial therapeutic paradigm for the treatment of HTN. However, additional research is needed to delineate the parameters by which it can be used without eliciting potentially unsafe increases in blood pressure.

Concerns are likewise raised with the claims that the BFR exercise technique may be beneficial to patients undergoing cardiac rehabilitation (106, 131, 166, 187). Madaramé et al. (106) had patients with stable ischemic heart disease perform low-intensity BFR exercise to assess changes in hemostatic and inflammatory markers. BFR did not affect exercise-induced changes in these specific markers, and, in the context of their findings, the authors suggested that low-intensity resistance exercise with BFR would be relatively safe for patients with ischemic heart disease. However, they also reported that plasma noradrenaline concentrations and HR were increased following BFR exercise, suggesting abnormal elevations in SNA. As with HTN, exercise has also been shown to be an effective treatment modality for HF. However, the level of exercise intensity considered to be safe is of great clinical concern. Will a patient with mild to moderate HF opt for the benefits of high-intensity resistance training (which they are unable and unprescribed to perform) by performing low-intensity resistance training with elastic bands on their thighs? Individuals performing BFR resistance training in HF may exhibit exaggerated muscle mechanoreflex- and metaboreflex-mediated increases in SNA. Indeed, EPR-mediated increases in SNA are exaggerated during mild-intensity exercise in HF, in the absence of BFR (56, 82, 137). Although it has been reported that skeletal muscle afferent feedback is downregulated in HF following aerobic exercise training (148), to our knowledge, no study has been conducted demonstrating this effect of training coupled with BFR. In any event, it is within the realm of possibility that further restriction of blood flow during BFR exercise in HF may exacerbate EPR-mediated increases in SNA and precipitate adverse cardiovascular events. As such, studies that are both carefully designed and performed are warranted before the general acceptance of BFR exercise as a safe method for cardiac rehabilitation.

One in 20 Americans over the age of 50 has PAD (29), and the frequency significantly increases with advancing age (29). The most common symptom of PAD is intermittent claudication, which often occurs during exercise but not under resting conditions (118). As such, many times PAD goes undiagnosed in the general clinical setting (115). As with HTN and HF, prescribed exercise is one of the primary treatments for individuals with this disease. BFR exercise has been proposed to be beneficial in the elderly to combat age-related loss of muscle mass and strength (2, 62, 67, 195, 215) and, potentially, could likewise be used to treat PAD. However, muscle metaboreflex-induced sympathetic responses are exaggerated during mild-intensity exercise in PAD, in the absence of BFR (89, 91, 130, 192). Heightened stimulation of muscle metaboreceptors attributable to the accumulation of metabolites and sensitization of mechanoreceptors are certainly major contributors to the exaggerated cardiovascular responses seen in disease states in which muscle perfusion is impaired, such as HF and PAD (89, 120). Moreover, in the rat model of human PAD, it has been shown that the expression of muscle metaboreceptors is upregulated following 24–72 h of ischemia induced by femoral arterial occlusion (89, 91, 209). Although BFR is employed on the order of several minutes rather than several hours, to our knowledge it is not known whether increases in muscle metaboreceptor expression can be initiated by a “typical bout” of BFR. Even so, further restriction of blood flow during BFR exercise in PAD may exacerbate EPR-mediated increases in SNA, elevating the risk for occurrence of an adverse cardiovascular event. Similar to the situations with HTN and HF, additional research is needed to determine whether BFR exercise can be used as a safe and effective therapy for PAD treatment.

Our principal apprehension for the implementation of BFR for treatment and rehabilitation purposes stems from a review by Loenneke et al. (92) addressing potential safety issues accompanying Kaatsu training. Although the review highlighted several potential concerns of which to be aware when using BFR training, there was no mention of the dangers inherent to individuals with HTN, HF, or PAD. Similarly, Nakajima et al. (131) performed a nationwide survey to assess the use and safety of BFR training. On the basis of the results of the study, it was concluded that Kaatsu training is safe. Moreover, the study suggested that it can be used by healthy individuals to increase muscle strength and size and is a promising method for enhancing the results derived from training in sports. The study also suggested that the method can be applied to persons with cerebrovascular disease, cardiac disease, and HTN. Despite the assertions of safety, the present review presents several scenarios in which pause and careful consideration of possible side effects should be considered before the adoption of BFR. Clearly the risks noted must be taken into account before the use of BFR training as a treatment or rehabilitative option in patients with HTN, HF, and PAD.

An additional concern with regard to the use of BFR training in patients with HTN, HF, and PAD is worth noting. The type of muscle fiber contracted plays a significant role in determining the sympathetically mediated cardiovascular response evoked by muscle reflex activation. For example, it has been demonstrated that contraction of fast-twitch glycolytic fibers
elicits a much larger pressor response than slow-twitch oxidative muscle (206). As discussed, BFR hastens the recruitment of fast-twitch fibers. As such, the use of BFR may generate markedly greater elevations in sympathetic activity and blood pressure than traditional exercise. Moreover, compared with normal healthy individuals, the percentage of fast-twitch fibers comprising skeletal muscle is enhanced in both patients with HTN and with HF (66, 90). This likely contributes to the muscle reflex overactivity manifest in each disease state. Given that BFR preferentially stimulates fast-glycolytic muscle, use of this technique likely exacerbates this reflex overactivity in these diseases.

Finally, it should be noted that, although EPR function is known to be altered in HTN, HF, and PAD, emerging evidence suggests that central command function may also be exaggerated in some of these disease states [e.g., HTN (34) and HF (22, 81, 132)]. Indeed, the perception of effort is enhanced during BFR exercise (44, 93, 97, 133, 150, 153, 199), which may potentiate central command-mediated increases in SNA and blood pressure. These potential alterations in central command function must likewise be taken into account when considering the implementation of BFR training in healthy individuals or after the advent of disease.

**BFR Training: Issues to Consider**

Although the founder of Kaatsu training stressed that BFR exercise should not be confused with exercise during ischemia (166), Sumide et al. (186) reported that an external cuff pressure of 50 mmHg around the thigh was a sufficient stimulus to restrict arterial blood flow (resulting in ischemia). Moreover, it is well documented that BFR training results in accumulation of metabolic byproducts of exercise such as lactate (46, 63, 77, 78, 110, 151, 187, 188, 212), which is a very potent stimulator of the muscle metaboreflex (35, 79, 155, 170, 175). Furthermore, much controversy persists over the “proper” external pressure required for the desired benefits of the maneuver (21, 68, 96, 97, 99, 100, 153). It is clearly not practical (or potentially even possible) to standardize a cuff pressure, as the amount of variables for which to adjust are seemingly limitless (e.g., differences in anatomy, vasculature, adiposity, muscle mass, etc.). Moreover, what method of mechanical occlusion of blood flow is the average individual employing in the typical fitness center in America, patented Kaatsu pressuring cuffs, elastic bands, rubber bands utilized in phlebotomy, makeshift devices? Indeed, an equal amount of controversy exists around BFR occlusion devices (96, 98, 100, 142, 153, 171, 215). Unlike the Kaatsu apparatus, which has a pressor sensor (166), it is virtually impossible to determine the degree of external pressure with the other aforementioned devices. This highlights a great concern for the degree of blood flow restriction that is being generated. For example, it has been reported that wider BFR cuffs restrict arterial blood flow at a lower cuff pressure than narrower BFR cuffs (28, 100, 153). Another confounding issue is that, in large part, pressurizing cuffs are made by different manufacturers using different materials (wider bands from nylon, narrower bands from elastic). Issues such as these punctuate our call for concern. Excessive restriction could indeed lead to significant ischemia as well as muscle “swelling” secondary to edema, both of which would likely suprastimulate the muscle mechanoreflex and metaboreflex even in healthy individuals. Moreover, excessive venous compression would elevate venous pressure, which could damage the valves in veins and lead to chronic venous insufficiency (38). As mentioned, although the building of skeletal muscle cannot be disputed, it is possible that misuse of this technique could lead to acute, abnormally large increases in sympathetic activity. These factors must be taken into consideration when adopting this technique for training.

Although individuals with certain cardiovascular diseases such as HTN, HF, and PAD are especially at risk for deleterious cardiovascular events when performing BFR training, our “call for concern” addresses the normal, healthy population as well. Healthy individuals performing intense resistance training exercise can achieve systolic and diastolic blood pressures well in excess of 300 mmHg (104, 143). In a study with young, healthy experienced bodybuilders, double-leg press evoked peak pressures of 320/240 mmHg, with one individual reaching 480/350 mmHg (104). Inasmuch as the EPR is engaged during even mild-intensity exercise (3, 7), enhanced stimulation of the EPR during intense resistance training exercise is certainly responsible for a significant portion of these alarming blood pressure responses. Although spikes in arterial blood pressure of this magnitude are certainly capable of producing adverse cardiovascular events (e.g., stroke, aneurysm, aortic dissection, and myocardial infarction), the risk for these deleterious outcomes is likely exacerbated when performing intense resistance training exercise coupled with BFR. Although altered EPR function in disease states such as HF, HTN, and PAD underlies our concern for these individuals performing BFR, the EPR response would likely be exaggerated even in normal, healthy individuals performing resistance training exercise with BFR compared with the same exercise with no occlusion. For example, as increases in metabolites in working muscle activate the afferent arm of the EPR, restricting arterial inflow and venous outflow via BFR during resistance training exercise would lead to elevations in these metabolites and therefore accentuate EPR-induced increases in sympathetic activity and arterial pressure (Fig. 4). As BFR exercise simulates high-intensity exercise during low-intensity conditions, the perception of effort is enhanced (44, 93, 97, 133, 150, 153, 199). Moreover, BFR exercise has been generally ascribed a high pain rating (59, 153, 202, 204, 205). Importantly, it is well documented that populations of group III and group IV afferents are responsive to pain stimuli (52, 74, 75, 84, 114, 116, 124). These factors may accentuate central command and EPR function, leading to abnormal elevations in SNA and MAP during BFR exercise in normal, healthy individuals.

As a final note, although elevated MAP is a powerful risk factor for vascular events, epidemiological evidence suggests that instability and variability in arterial blood pressure are important risk factors as well (154). To this point, a diurnal, midmorning surge of arterial blood pressure is predictive of stroke (69) yet is poorly associated with MAP (69, 207). This suggests that it is the spike in arterial pressure per se that triggers the vascular events. In spontaneously hypertensive rats, increased short-term variability in arterial blood pressure causes ischemic stroke and other end-organ damage (119). Sinoaortic denervation in the rat, which markedly increases variability in blood pressure without changing MAP, causes
left ventricular hypertrophy and aortic vasoconstriction (168). Moreover, transient increases in arterial blood pressure secondary to sympathetic overactivity are also associated with increased vascular risk (40, 70). Although data on reflected arterial waveforms show that vascular changes appear to be localized within the involved musculature, with no demonstration of positive (or negative) effects on large-vessel stiffness, augmentation index, or central aortic blood pressure, to our knowledge, the correlation between BFR-induced spikes in arterial pressure and risk for cardiovascular events is unknown. However, a very recent retrospective analysis identified normal individuals at risk for cardiovascular events as indexed by adverse blood pressure responses during BFR training (95).

Conclusion

In summary, the use of BFR training can clearly increase muscle mass and strength, along with endurance. Implemented properly and with appropriate supervision, this form of training could be potentially beneficial, not only to normal healthy individuals, but also as a form of treatment and rehabilitation therapy for conditions in which loss of muscle mass and strength is debilitating. That being stated, further research is needed before this type of training can be fully endorsed. For example, the optimal duration and intensity of pressure cuff-induced skeletal muscle blood flow restriction must be determined, and the effect of longer-term use needs to be evaluated. Moreover, given concerns that excessive restriction could lead to overactivation of muscle reflexes and/or central command with consequent development of sympathetic hyperreactivity and increased risk for cardiovascular-related adverse events, the safety of Kaatsu methods must be tracked. This is particularly true for individuals with established cardiovascular disease (e.g., HTN, HF, and PAD), as even appropriate use of blood flow restriction techniques could lead to clinical deterioration attributable to intermittent sympathetic overactivity and blood pressure elevation. The latter is of considerable concern given the prevalence of undiagnosed and uncontrolled HTN and PAD within the US population. To avoid untoward outcomes and ensure that BFR exercise is properly used, efficacy endpoints such as those focused on maximal force generation and exertional capacity must be balanced with safety measures, particularly the incidence of adverse cardiovascular (e.g., acute myocardial infarction and acute pulmonary edema) and cerebrovascular (e.g., ischemic or hemorrhagic stroke) events.

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