

## **Low intensity blood flow restriction exercise: Rationale for a hypoalgesia effect**

Luke Hughes<sup>1</sup> PhD and Stephen David Patterson<sup>1</sup> PhD

<sup>1</sup> Faculty of Sport, Health and Applied Science, St Mary's University, London, UK, TW1 4SX\*

Corresponding author:

Luke Hughes

luke.hughes@stmarys.ac.uk

\* = address for corresponding author

Source of support: None

## **SUMMARY**

Exercise-induced hypoalgesia is characterised by a reduction in pain sensitivity following exercise. Recently, low intensity exercise performed with blood flow restriction has been shown to induce hypoalgesia. The purpose of this manuscript is to discuss the mechanisms of exercise-induced hypoalgesia and provide rationale as to why low intensity exercise performed with blood flow restriction may induce hypoalgesia. Research into exercise-induced hypoalgesia has identified several potential mechanisms, including opioid and endocannabinoid-mediated pain inhibition, condition pain modulation, recruitment of high threshold motor units, exercise-induced metabolite production and an interaction between cardiovascular and pain regulatory systems. We hypothesise that several mechanisms consistent with prolonged high intensity exercise may drive the hypoalgesia effect observed with blood flow restriction exercise. These are likely triggered by the high level of intramuscular stress in the exercising muscle generated by blood flow restriction including hypoxia, accumulation of metabolites, accelerated fatigue onset and ischemic pain. Therefore, blood flow restriction exercise may induce hypoalgesia through similar mechanisms to prolonged higher intensity exercise, but at lower intensities, by changing local tissue physiology, highlighting the importance of the blood flow restriction stimulus. The potential to use blood flow restriction exercise as a pain modulation tool has important implications following acute injury and surgery, and for several load compromised populations with chronic pain.

## INTRODUCTION

Exercise is known to decrease sensitivity to pain, an endogenous form of pain modulation termed ‘exercise-induced hypoalgesia’ (EIH) [1]. In the exercising muscle, EIH is reported following acute bouts of resistance [2], aerobic [3] and isometric exercise [4,5], with several review articles summarising this research [1,6–9]. Pain desensitisation following exercise is not limited to the exercising limb, and is observed in non-exercising muscles in remote areas of the body [10–14] to a smaller extent than the exercising muscle [10,15,16]. This suggests that both local manifestations and spinal/supraspinal nociceptive pathways drive a multisegmental pain inhibitory effect with exercise.

EIH is commonly examined by measuring either pain threshold (i.e. when a noxious stimulus is first perceived as painful) or pain tolerance (i.e. suprathreshold pain intensity ratings) [8]. A number of different noxious stimuli are used to induce pain, including temperature, electrical, ischemic and mechanical pressure stimulation [8]. For resistance, aerobic and isometric exercise the existing literature suggests there is a moderate to large effect for EIH in healthy and chronic pain populations ( $d=0.41-1.02$ ) [8]. Similar to other exercise-induced adaptations such as increased muscle strength, the magnitude of EIH appears to be augmented with higher intensity exercise [10,17–19]. For resistance exercise, a large effect ( $d=0.6-1.1$ ) of EIH is observed with high intensity exercise using an external load of 75% of one repetition maximum (1RM) [2,19]. Aerobic exercise performed at a higher intensity (i.e.  $>75\%$  of maximal oxygen uptake) and for longer duration ( $>10$  minutes) appears to elicit greater EIH [8,18].

Though aerobic and resistance exercise typically lead to hypoalgesia in pain-free adults, hyperalgesia may be observed in certain individuals with chronic pain [20]. Nevertheless, the palliative effect of exercise is useful in pain management programmes, particularly due to its accessibility and cost-effectiveness. Current evidence demonstrates the effectiveness of both resistance and aerobic exercise for relieving pain in people with fibromyalgia [21], osteoarthritis [22] and chronic neck and back pain [23]. High intensity exercise that can stimulate muscle, bone and cardiovascular adaptations [24–26] while also reducing pain therefore has a dual effect for populations with chronic pain. However, load compromised populations such as older adults or those undergoing rehabilitation following injury often cannot withstand the stress of high intensity

exercise. In addition, high intensity exercise may cause more pain in individuals with chronic pain [20]. In these situations, alternative options using low intensity exercise have been explored. One such alternative is blood flow restriction (BFR) exercise which involves partial and full restriction of arterial and venous blood flow, respectively, in the exercising limb during low intensity exercise [27]. BFR is achieved using a pneumatic tourniquet cuff placed proximally on the limb, which when inflated compresses the underlying vasculature resulting in venous blood pooling and an ischemic and hypoxic environment in the tissues below and distal to the cuff [28]. BFR during low intensity (20-30% 1RM) resistance training stimulates greater muscle hypertrophy and strength adaptations compared to matched workload exercise without BFR [29], and these adaptations are comparable to high intensity (>70% 1RM) resistance training [30–33]. Aerobic exercise (i.e. walking and cycling) of low intensity (i.e. <40% of maximal oxygen uptake) with BFR has been shown to increase muscle hypertrophy and strength [34,35], which does not normally occur in response to low intensity aerobic training [35,36]. Though low intensity resistance exercise to concentric failure may stimulate muscle hypertrophy adaptations similar to high intensity resistance training [37], this does not appear to be the case for muscle strength or aerobic exercise [38,39]. Moreover, performing low-intensity exercise to concentric failure likely involves prolonged durations that may not be feasible for individuals recovering from injury, whereas BFR accelerates the development of muscle fatigue during low intensity exercise [40]. BFR exercise is therefore widely regarded as a beneficial rehabilitation tool for load compromised and rehabilitating populations [41].

BFR exercise has been shown to reduce pain across a training programme in a range of clinical conditions [30,31,42]. Recent evidence shows EIH occurs when low intensity exercise (e.g.  $\leq 30\%$  1RM) is performed with BFR [43,44]. A single bout of low intensity knee extension exercise with BFR was found to reduce anterior knee pain immediately post-exercise. This moderate to large effect was sustained for a minimum of 45 minutes [43,44]. For load compromised and rehabilitating populations with chronic pain that cannot withstand high intensity exercise or low intensity exercise to failure, BFR exercise would therefore have a dual effect for pain and other adaptations. For example, BFR exercise has recently been shown to improve pain reduction and physical function to a greater extent than heavy load resistance training in individuals with rheumatoid arthritis [45] and following surgery for ligament repair [46].

As EIH is associated with prolonged high intensity exercise, the mechanisms driving EIH with low intensity BFR exercise may be different or triggered in a different manner. Therefore, exploration of the potential mechanisms and efficacy of BFR exercise with respect to EIH is warranted prior to future research. The purpose of this manuscript is to discuss the mechanisms behind EIH and provide a rationale as to how BFR during low intensity exercise may trigger EIH.

## **MECHANISMS OF EXERCISE-INDUCED HYPOALGESIA**

Though chronic exercise may reduce pain through changes in cognitive appraisal of a noxious stimulus [47], a reduction in pain following acute exercise suggests that changes must occur within the peripheral and/or central nociceptive pathways. Whether these changes are predominately peripheral, central or both is not fully understood [48], and both human and animal research indicates there are several analgesia mechanisms that contribute to EIH. This includes: opioid and non-opioid driven pain-inhibition [6,7,49–52]; interaction of the cardiovascular and pain regulatory systems [8,53–57]; conditioned pain modulation [4,10,58,59]; metabolite-induced pain [60] and recruitment of high threshold motor units [11]. The following sections provide an overview of the mechanisms contributing to hypoalgesia with exercise.

### **Activation of the endogenous opioid system**

Exercise-induced stimulation of endogenous opioid production is the most commonly proposed mechanism of pain desensitisation following exercise [6,50]. EIH is thought to be driven in part by beta-endorphin, an endogenous opioid neuropeptide that is one of the most prominent in the opioid peptide family. Beta-endorphin is produced in peripheral neurons and in the pituitary gland within the CNS in response to physiological stressors such as pain and exercise. It serves as an agonist for opioid receptors throughout the CNS and PNS, particularly of the mu subtype. These receptors are found in abundance within the central terminals of primary afferent neurons and peripheral sensory nerve fibres within the PNS [61] and descending pain control circuits in the CNS [62]. Beta-endorphin binds to opioid receptors at pre- and post-synaptic terminals [63] to cause a profound inhibition of noxious-evoked activity peripherally, spinally and supraspinally. Elevations in peripheral blood beta-endorphin concentrations have been reported in humans

following exercise [7,64], which is thought to be caused by stimulation of group III and IV primary afferents in the contracting muscle. This in turn activates the opioid system [7] and modulates pain via spinal and/or supraspinal inhibitory mechanisms [46], which may drive pain desensitisation in non-exercising and remote muscles [10]. Several studies reporting attenuation of EIH following administration of an opioid antagonist such as naloxone or naltrexone in humans [65,66] and animals [67] support the role of the opioid system in EIH [1].

### **Endocannabinoid-mediated mechanisms**

Evidence of hypoalgesia that is insensitive to opioid antagonists suggests that EIH must be mediated in part by non-opioid mechanisms [6]. One such mechanism may involve the endocannabinoid system [68]. This system consists of the endogenous ligand agonists N-arachidonyl ethanolamide (AEA) and 2-arachidonoylglycerol (2-AG), G-protein-coupled cannabinoid (CB) receptors CB1 and CB2 (type 1 and 2, respectively) and metabolising enzymes. Endocannabinoids have been shown to have antinociceptive effects in models of acute pain in animals and humans [69,70] by binding to CB1 and CB2 receptors found in the PNS and at spinal and supraspinal pain processing sites [68,69]. Endocannabinoids are synthesised from arachidonic acid and can be released from cells immediately after their synthesis [71] in response to stress of a physical nature [49]. Several studies have observed systemic elevations in circulating concentrations of AEA following exercise [52,71–73], suggesting endocannabinoids play a role in EIH. This would be supported by the dense expression of CB receptors on A-delta and C-delta primary afferents [74] which are activated during muscle contractions to produce alterations in circulating concentrations of endocannabinoids [6]. Similarly to opioid-mediated mechanisms, the mechanisms of analgesia driven by endocannabinoids likely include inhibition of presynaptic neurotransmitter and neuropeptide release and activation of the descending pain inhibitory pathway [68].

### **Interaction of cardiovascular and pain regulatory systems**

Several lines of evidence suggest that a link and interaction between the cardiovascular and pain modulatory systems acts as a mechanism of EIH [8,53–57], in particular the control of blood pressure. Brain regions

underlying control of the cardiovascular system through aspects such as baroreceptors overlap substantially with the regions contributing to antinociception [54,75]. This includes the same brain stem nuclei [54,76], neurotransmitters and opioid neuropeptides [75,77]. In the absence of exercise, hypoalgesia is associated with chronically elevated blood pressure in hypertensive individuals [54,78] which may be partly mediated in the CNS by elevated central descending pain inhibitory activity [79]. Moreover, in healthy normotensive individuals higher resting blood pressure is associated with decreased sensitivity to noxious stimuli [80,81]. Though less research has examined the interaction of blood pressure, hypoalgesia and exercise, it demonstrates that decreased sensitivity to noxious stimuli is observed in conjunction with exercise-induced increases in heart rate and blood pressure [77,82,83].

Currently the mechanisms are not fully understood, however it is suggested that baroreceptors and endogenous opioids may be involved in this interaction between exercise, blood pressure and pain perception [53]. Regarding baroreceptors, a functional model of this relationship suggests that increased blood pressure during exercise through sympathetic arousal leads to increased baroreceptor stimulation. This in turn triggers descending inhibitory activity in an effort to restore homeostasis [54,77,84]. A number of studies have demonstrated an exercise-induced increase in blood pressure concurrent with a decrease in pain perception [53,55,56] that is consistent with an arterial baroreceptor inhibition mechanism for EIH [10,54]. Moreover, the association between elevated resting blood pressure and reduced sensitivity to noxious stimuli [54,78,80] may reflect inhibitory baroreceptor effects on the CNS [10,85,86]. Regarding endogenous opioids, several animal studies have demonstrated that an opioid blockade reverses the decreased pain sensitivity observed with hypertension [54], however findings from human research are equivocal [53].

### **Conditioned pain modulation**

It is proposed that diffuse noxious inhibitory controls [13] may contribute to EIH [58]. This endogenous supraspinal pain inhibitory mechanism is more commonly referred to as ‘conditioned pain modulation’ (CPM), which describes a phenomenon where pain inhibits pain [58,87]. This mechanism is activated when two noxious stimuli are applied to two different areas of the body [58]. The initial noxious stimulus, known as the conditioning stimulus, triggers inhibition of extra-segmental spinal and trigeminal wide dynamic range

neurons to reduce the perception of the second noxious stimulus [10,58,59,88]. Similarly to EIH, reduced pain sensitivity following CPM has been shown to extend beyond the initial noxious stimulus [1,89]. Systemic hypoalgesia is observed with both CPM and EIH [10,59], and similarly to the characteristics of EIH the stronger the initial noxious stimulus with CPM the greater the reduction in pain sensitivity to the test stimulus [89,90]. Research suggests CPM and EIH may use similar mechanisms. In individuals with osteoarthritis, Fingleton et al. [91] demonstrated that abnormal CPM, which reflects central hypersensitivity with osteoarthritis, resulted in dysfunctional EIH following aerobic and isometric exercise. However, normal EIH functioning was observed in individuals with an efficient CPM response [91].

CPM itself may be a mechanism of EIH with exercise acting as a noxious conditioning stimulus to activate descending inhibitory pathways [13,14]. CPM has been shown to predict EIH in both young and older pain-free adults [59], and research demonstrates that EIH is greater following painful isometric and aerobic exercise compared to non-painful exercise in pain-free individuals [11,58]. More recently, Ellingson et al. [58] found that pain sensitivity to a noxious heat stimulus decreased to a greater magnitude following painful exercise compared to non-painful exercise, with no change in a resting condition. As EIH was still observed with non-painful exercise, this suggests that CPM may not be the primary mechanism driving EIH but likely contributes to the overall hypoalgesia effect.

### **Exercise-induced metabolites**

Research has demonstrated the importance of exercise-induced metabolites in pain perception, including adenosine triphosphate (ATP), lactate and protons [60]. These metabolites are known to stimulate a subset of dorsal root ganglion group III and IV nociceptive afferent neurons in skeletal muscle [92–94]. This is demonstrated by activation of these neurons with intramuscular infusion of supraphysiological concentrations of such metabolites [95]. As outlined by Pollak et al. [60] one subset of these neurons responds to the level of metabolites produced during non-painful exercise and potentially contributes to the exercise pressor reflex [96]. The other subset responds to the level of metabolites that only occur during high-intensity muscle contractions and ischemia, and thus may contribute to acute muscle pain during exercise. It is thought that group III and IV muscle afferents signal metabolite production in skeletal muscle



using a complex of acid sensing ion current (ASIC), purinergic detecting (P2X) and transient receptor potential channel (TRP) receptors [60], whose endogenous muscle agonists are combinations of ATP, lactate and protons. Pollak et al. [60] infused physiological concentrations of these agonists to muscle interstitium, including combinations found in resting muscles and during both moderate and vigorous exercise. The authors reported that metabolite combinations found in resting muscle evoked no sensation of pain. They also found that intramuscular infusion of a combination of these agonists increased pain sensation in a dose-dependent manner, likely through activation of ASIC, P2X and TRP receptors. Metabolite production and subsequent activation of group III and IV nociceptive afferent neurons to create acute muscle pain during exercise may therefore act as a noxious conditioning stimulus and induce EIH in a CPM manner.

### **High threshold motor unit recruitment**

More pronounced EIH with prolonged higher intensity exercise [17–19] may be due in part to the recruitment of high threshold motor units. During prolonged high intensity exercise the majority of force output is provided by high threshold motor units, leading to suggestions that recruitment of this fibre type is a mechanism for EIH [11]. Support for this hypothesis arises from research examining EIH with isometric exercise [11,13,97,98]. Interestingly, perception of pain to a noxious thermal stimulus has been found to be unchanged after both low and high intensity isometric contractions of a short duration (<2-3 minutes)[99,100]. In contrast, a decrease in pain sensitivity has been observed following low intensity isometric contractions of lower and upper limb muscles performed for longer duration (>3 minutes) or to volitional failure [4,5,10,13,97,101]. This suggests that EIH may be dependent on both the intensity and duration of exercise [8]. Most recently this was demonstrated by Hoeger-Bement et al. [11] who examined the dose response of isometric exercise of varying intensity and duration on pain perception to mechanically induced pain in the elbow flexor muscles. In a crossover design, participants performed: 1) Three maximal voluntary contractions (MVC) for a short duration; 2) 25% MVC until volitional failure; 3) 25% MVC for short duration (<2 minutes); and 4) 80% MVC until volitional failure. Though hypoalgesia is not typically induced by low intensity muscle contractions, the authors observed hypoalgesia with both high and low intensity contractions performed until volitional failure. During isometric contractions of a longer duration (i.e. >3 minutes or to failure) active motor units become fatigued and high threshold motor units are recruited

to maintain force output [102], which may explain the greater hypoalgesia effect. This would be supported by other studies demonstrating hypoalgesia when low-intensity isometric contractions were performed for >3 minutes or to volitional failure [13,16,97,98]. Together, this body of work suggests that activation of high-threshold motor units is involved in EIH.

## **BFR EXERCISE AND HYPOALGESIA**

Low intensity exercise performed with BFR has recently been shown to trigger hypoalgesia. In patients with anterior knee pain, Korakakis et al. [43,44] investigated the effect of four sets of low intensity open kinetic chain knee extension exercise with BFR on knee pain prior to a physiotherapy session. Knee pain was measured during several exercises using a numerical pain rating scale. An immediate and clinically significant reduction in knee pain was observed following BFR exercise, which was sustained after a 45-minute physiotherapy session. Chronic reductions in knee pain over the course of a resistance training programme have been observed with low intensity BFR exercise [30,31], which may be driven by less pain during BFR exercise [33,103] and repeated exposure to the acute hypoalgesia effect [43,44] as seen in non-injured populations [47]. Given that hypoalgesia appears to be augmented by higher intensity (and longer duration) exercise and is not typically observed with low intensity exercise, it is important to explore the potential mechanisms driving hypoalgesia with low intensity BFR exercise. An overview of the potential mechanisms is provided in Figure 1.

One potential mechanism by which low intensity BFR exercise may trigger hypoalgesia is activation of the opioid and endocannabinoid systems. During BFR exercise the inflated cuff partially restricts arterial blood flow to the limb, causing an ischemic and hypoxic state in tissues below and distal to the cuff [28]. As veins require less external pressure to fully occlude, there is complete restriction of venous outflow from the muscle. It has been shown that addition of BFR during low intensity (20% 1RM) exercise significantly increases metabolic stress compared to matched exercise without BFR, indicated by intramuscular accumulation of exercise-induced metabolites and a reduction in pH [104]. Elevated concentrations of metabolites and the associated acidification stimulates muscle chemoreceptors [105] which may activate group III and IV afferent fibres [106], altering afferent feedback to the CNS. Furthermore, there is an acute

increase in muscle pain/discomfort with BFR exercise [107,108] which may be caused by metabolite-induced stimulation of group III and IV afferent fibres and increased sympathetic nervous activity [109], resulting in an increased perception of pain/discomfort. This may activate both the opioid and endocannabinoid systems to trigger hypoalgesia. For example, beta-endorphin is produced in the PNS and CNS in response to both pain and exercise. This is believed to be caused by stimulation of group III and IV primary afferents in the contracting muscle, which then activates the opioid system [7] and modulates pain via spinal and/or supraspinal inhibitory mechanisms [46]. Similarly, endocannabinoids are released from their synthesising cells in response to physical stress [49]. Therefore, increasing the level of metabolic stress in the muscle by using BFR during low intensity exercise may trigger both opioid and endocannabinoid-mediated mechanisms of hypoalgesia.

A second potential mechanism by which BFR exercise may elicit hypoalgesia is through CPM. Though low intensity exercise (not to failure) is not typically described as painful, it is well documented that the perception of pain and discomfort is augmented during BFR exercise [110] to a similar extent as high intensity exercise [111,112]. Painful exercise may act as a noxious conditioning stimulus to activate descending inhibitory pathways [13,14], and the level of hypoalgesia appears to be greater following painful exercise compared to non-painful exercise [11,58]. With BFR exercise, it is thought that stimulation of group III and IV afferent fibres increases sympathetic nervous activity to increase perception of pain/discomfort [109]. Given the considerable level of muscle pain that is characteristic of BFR exercise, the exercise itself may act a noxious conditioning stimulus to activate descending inhibitory pathways [43,44]. Related to this, the importance of exercise-induced metabolites in pain perception through activation of group III and IV nociceptive afferent neurons has been described [92–94]. As highlighted by Pollack et al. [60], one subset of group III and IV nociceptive afferent neurons in skeletal muscle responds to the level of metabolites that only occur during high intensity muscle contractions and ischemia. Though BFR exercise is performed at a low intensity, the tissues of the involved limb are ischemic due to the reduction in arterial blood flow to the limb. Therefore, the level of metabolic stress generated during low intensity BFR exercise and subsequent activation of group III and IV nociceptive neurons to create a high level of pain may act as a noxious conditioning stimulus to elicit hypoalgesia in a CPM manner. Application of a tourniquet alone in cyclic fashion may also induce hypoalgesia. Cyclic restriction of limb blood flow has been shown to reduce pain

following surgery, when applied both post-operatively [113] and perioperatively [114]. Moreover, cyclic application of BFR following an acute bout of muscle damage inducing exercise has been shown to reduce muscle soreness [115]. CPM driven pain reduction may be related to hypoxia or inflammation per se, and possibly achievable with BFR in the absence of exercise.

A third potential mechanism by which BFR exercise may trigger hypoalgesia is the early preferential recruitment of high threshold motor units. Recruitment of high threshold motor units is hypothesised to be an important mechanism of EIH [11], and may explain why a greater hypoalgesia effect is observed with prolonged high intensity exercise [17–19]. High threshold motor units are typically only recruited at high intensities of work, with low threshold motor units providing force output during low intensity exercise [116]. With BFR exercise this principle appears to be reversed and high threshold motor units are preferentially recruited early during exercise [117,118]. This is likely due to the hypoxic muscular environment generated during BFR and accelerated onset of fatigue [117]. Several studies have shown greater internal muscle activation with BFR exercise [119,120] relative to external load [121,122], which is greater than matched workload exercise without BFR [123,124]. Considering the importance of high threshold motor unit recruitment to the magnitude of EIH, early preferential recruitment of these motor units during low intensity BFR exercise may contribute to a hypoalgesia effect.

The link between the cardiovascular and pain modulatory systems may provide another mechanism by which BFR exercise elicits hypoalgesia. Higher blood pressure and heart rate during both rest and exercise is associated with decreased sensitivity to noxious stimuli [54,77,78,82,83]. This may be due to the overlap in the areas of the brain controlling baroreceptors and nociception [54,75]. During exercise, increased blood pressure leads to increased baroreceptor stimulation which then triggers descending inhibitory activity in an effort to restore homeostasis [54,77,84]. Exercise-induced increases in heart rate and blood pressure are amplified with BFR exercise compared to matched workloads without BFR [125–127] when exercise is not performed until volitional failure. These changes may be similar or greater than those observed during high intensity exercise [111,128,129]. It has been proposed that mechanical compression of the vasculature during BFR exercise may augment the exercise-induced pressor response [130], leading to an increase in heart rate and blood pressure. If a link between blood pressure, baroreceptors and pain modulation does exist, it is

conceivable that an augmented increase in heart rate and blood pressure during BFR exercise may trigger hypoalgesia through greater baroreceptor stimulation and subsequent activation of descending inhibitory pathways. Currently, this potential mechanism is not fully understood and further research to examine this is warranted.

## **PERSPECTIVES & RESEARCH RECOMMENDATIONS**

Studies published thus far support the hypothesis that low intensity BFR exercise may trigger significant hypoalgesia. The limited number of studies available and lack of understanding of the mechanisms provide rationale for future research. Ultimately, an important goal would be to develop BFR exercise as a pain management tool for populations with chronic pain. However, prior to this a number of areas must be investigated. Acute training studies are needed to compare the magnitude of hypoalgesia with BFR exercise to equivalent forms of exercise at both low and high intensities. Moreover, investigation of the mechanisms underpinning hypoalgesia with BFR exercise is required to develop our understanding of EIH. For example, a study could be conducted to investigate the effects of BFR exercise on hypoalgesia compared to equivalent forms of exercise at both low and high intensities while measuring concentrations of circulating blood opioid and endocannabinoid markers, muscle pain, blood pressure, muscle activation and metabolite production. Measuring the degree of each of these variables would test the hypothesis that hypoxia, metabolite accumulation and early onset of fatigue trigger hypoalgesia with BFR exercise via similar mechanisms to prolonged high intensity exercise. This may also allow for optimisation of any effect in the future. Importantly, existing research has not examined if BFR exercise also causes systemic hypoalgesia or if the effect is limited to the exercising muscles. Long term training studies are needed to determine whether acute decreases in pain sensitivity translate into chronic reductions in pain with BFR exercise.

It is also of importance to note that the studies completed thus far have used numerical pain rating scales to measure pain [43,44]. More objective measures are needed for future research, for example by measuring pain thresholds and tolerance using pressure, thermal and electrical stimuli [8]. Prescription and selection of BFR pressure has been shown to influence several aspects related to BFR exercise including training adaptations [131] and the acute physiological responses [132]. It is important that prescription of BFR pressure is personalised to each individual as a percentage of limb occlusion pressure [133]. For example, though the impact of different cuff sizes and pressures on the EIH response is unknown, existing literature shows that higher cuff pressures induce greater pain during BFR exercise. If CPM is a mechanism by which BFR exercise triggers hypoalgesia, then the pressure applied would likely be an important variable to consider with respect to EIH.

sIn conclusion, we hypothesise that several mechanisms consistent with prolonged high intensity exercise may drive the hypoalgesia response observed with low intensity BFR exercise. These are likely triggered by the level of stress in the exercising muscle generated by BFR including hypoxia, metabolite accumulation. early onset of fatigue and ischemic pain.

#### **Conflict of interest statement**

Neither authors report any conflicts of interest.

#### **Acknowledgements**

No funding was received specifically in support of this review.

## References

- [1] Koltyn KF. Analgesia following exercise: A review. *Sport Med* 2000;29:85–98. doi:10.2165/00007256-200029020-00002.
- [2] Focht BC, Koltyn KF. Alterations in pain perception after resistance exercise performed in the morning and evening. *J Strength Cond Res* 2009;23:891–7. doi:10.1519/JSC.0b013e3181a05564.
- [3] Vaegter HB, Kathrine L, Mia B, Redin M, Hartung S, Nielsen TG. Hypoalgesia after bicycling at lactate threshold is reliable between sessions. *Eur J Appl Physiol* 2018;19:91–102. doi:10.1007/s00421-018-4002-0.
- [4] Alsouhibani A, Vaegter HB, Bement MH. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. *Pain Med* 2019;20:180–90. doi:10.1093/pm/pny057.
- [5] Vaegter HB, Lyng KD, Yttereng FW, Christensen MH, Sørensen MB, Graven-Nielsen T. Exercise-Induced Hypoalgesia After Isometric Wall Squat Exercise: A Test-Retest Reliability Study. *Pain Med* 2019;20:129–37. doi:10.1093/pm/pny087.
- [6] Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C. Mechanisms of Exercise-Induced Hypoalgesia. *J Pain* 2014;15:1294–304. doi:10.1016/j.jpain.2014.09.006.Mechanisms.
- [7] Thoren P, Floras JS, Hoffman P, Seals DR. Endorphins and exercise: physiological mechanisms and clinical implications. *Med Sci Sport Exerc* 1990;22:417-428. doi:10.1249/00005768-199008000-00001.
- [8] Naugle KM, Fillingim RB, Riley JL. A Meta-Analytic Review of the Hypoalgesic Effects of Exercise. *J Pain* 2012;13:1139–50. doi:10.1016/j.jpain.2012.09.006.
- [9] Polaski AM, Phelps AL, Kostek MC, Szucs KA, Kolber BJ. Exercise-induced hypoalgesia: A meta-analysis of exercise dosing for the treatment of chronic pain. *PLoS One* 2019;14:e0210418. doi:https://doi.org/10.1371/journal.pone.0210418 Editor:
- [10] Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain* 2013;155:158–67. doi:10.1016/j.pain.2013.09.023.
- [11] Hoeger-Bement MK, Dicapo J, Rasiarmos R, Hunter SK. Dose Response of Isometric Contractions on Pain Perception in Healthy Adults. *Med Sci Sport Exerc* 2008;40:1880–9. doi:10.1249/MSS.0b013e31817eecc.
- [12] Koltyn KF, Umeda M. Contralateral Attenuation of Pain After Short-Duration Submaximal Isometric Exercise. *J Pain* 2007;8:887–92. doi:10.1016/j.jpain.2007.06.003.



- [13] Kosek E, Lundberg L. Segmental and plurisegmental modulation of pressure pain thresholds during static muscle contractions in healthy individuals. *Eur J Pain* 2003;7:251–8. doi:10.1016/S1090-3801(02)00124-6.
- [14] Lemley KJ, Drewek B, Hunter SK, Bement MKH. Pain Relief after Isometric Exercise Is Not Task-Dependent in Older Men and Women. *Med Sci Sport Exerc* 2013;46:185–91. doi:10.1249/MSS.0b013e3182a05de8.
- [15] Micalos PS, Nielsen LA. Differential pain response at local and remote muscle sites following aerobic cycling exercise at mild and moderate intensity. *Springerplus* 2016;5:eCollection 2016. doi:10.1186/s40064-016-1721-8.
- [16] Naugle KM, Naugle KE, Fillingim RB, Riley JL. Isometric exercise as a test of pain modulation: Effects of experimental pain test, psychological variables, and sex. *Pain Med* 2014;15:692–701. doi:10.1111/pme.12312.
- [17] Koltyn KF. Exercise-Induced Hypoalgesia and Intensity of Exercise. *Sport Med* 2002;32:477–87.
- [18] Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS. Intensity and Duration Threshold for Aerobic Exercise-Induced Analgesia to Pressure Pain. *Arch Phys Med Rehabil* 2003;85:1183–1187. doi:10.1016/j.apmr.2003.09.010.
- [19] Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. *Br J Sports Med* 1998;32:20–4.
- [20] Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, et al. Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions. *J Pain* 2019;0:1–18. doi:10.1016/j.jpain.2019.03.005.
- [21] Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenswolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 2010;12:R79. doi:10.1186/ar3002.
- [22] Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJM, de Bie Rob A. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review. *J Physiother* 2011;57:11–20. doi:10.1016/S1836-9553(11)70002-9.
- [23] Cuesta-Vargas AI, González-Sánchez M, Casuso-Holgado MJ. Effect on health-related quality of life of a multimodal physiotherapy program in patients with chronic musculoskeletal disorders. *Health Qual Life Outcomes* 2013;11:1–8. doi:10.1186/1477-7525-11-19.

- [24] Kraemer WJ, Ratamess NA. Fundamentals of Resistance Training: Progression and Exercise Prescription. *Med Sci Sports Exerc* 2004;36:674–88. doi:10.1249/01.MSS.0000121945.36635.61.
- [25] Nevill AM, Holder RL, Stewart AD, Nevill AM, Holder RL, Stewart AD, et al. Do sporting activities convey benefits to bone mass throughout the skeleton? Do sporting activities convey benefits to bone mass throughout the skeleton? *J Sports Sci* 2004;22:645–50. doi:10.1080/02640410310001655769.
- [26] Hellsten Y, Nyberg M. Cardiovascular Adaptations to Exercise Training. *Compr Physiol* 2015;6:1–32. doi:10.1002/cphy.c140080.
- [27] Scott BR, Loenneke JP, Slattery KM, Dascombe BJ. Exercise with Blood Flow Restriction: An Updated Evidence-Based Approach for Enhanced Muscular Development. *Sport Med* 2015;45:313–25. doi:10.1007/s40279-014-0288-1.
- [28] Manini TM, Clark BC. Blood flow restricted exercise and skeletal muscle health. *Exerc Sport Sci Rev* 2009;37:78–85. doi:10.1097/JES.0b013e31819c2e5c.
- [29] Loenneke JP, Wilson JM, Marín PJ, Zourdos MC, Bembien MG. Low intensity blood flow restriction training: A meta-analysis. *Eur J Appl Physiol* 2012;112:1849–59. doi:10.1007/s00421-011-2167-x.
- [30] Ferraz RB, Gualano B, Rodrigues R, Kurimori CO, Fuller R, Lima FR, et al. Benefits of Resistance Training with Blood Flow Restriction in Knee Osteoarthritis. *Med Sci Sport Exerc* 2017;50:897–905. doi:10.1249/MSS.0000000000001530.
- [31] Giles L, Webster KE, McClelland J, Cook JL. Quadriceps strengthening with and without blood flow restriction in the treatment of patellofemoral pain: A double-blind randomised trial. *Br J Sports Med* 2017;51:1688–94. doi:10.1136/bjsports-2016-096329.
- [32] Ladlow P, Coppack RJ, Dharm-Datta S, Conway D, Sellon E, Patterson SD, et al. Low-Load Resistance Training With Blood Flow Restriction Improves Clinical Outcomes in Musculoskeletal Rehabilitation: A Single-Blind Randomized Controlled Trial. *Front Physiol* 2018;9:1–14. doi:10.3389/fphys.2018.01269.
- [33] Bryk FF, dos Reis AC, Fingerhut D, Araujo T, Schutzer M, Cury R de PL, et al. Exercises with partial vascular occlusion in patients with knee osteoarthritis: a randomized clinical trial. *Knee Surgery, Sport Traumatol Arthrosc* 2016;24:1580–6. doi:10.1007/s00167-016-4064-7.
- [34] Abe T, Kearns CF, Fujita S, Sakamaki Y, Sato Y, Brechue WF. Skeletal muscle size and strength are increased following walk training with restricted leg muscle blood flow: implications for training duration and frequency. *Int J KAATSU Train Res* 2009;5:9–15. doi:10.3806/ijktr.5.9.
- [35] Ozaki H, Sakamaki M, Yasuda T, Fujita S, Ogasawara R, Sugaya M, et al. Increases in thigh muscle

- volume and strength by walk training with leg blood flow reduction in older participants. *Journals Gerontol* 2011;66 A:257–63. doi:10.1093/gerona/glq182.
- [36] Abe T, Kearns CF, Sato Y. Muscle size and strength are increased following walk training with restricted venous blood flow from the leg muscle, Kaatsu-walk training. *J Appl Physiol* 2006;100:1460–6. doi:10.1152/japplphysiol.01267.2005.
- [37] Ogasawara R, Loenneke JP, Thiebaud RS, Abe T. Low-Load Bench Press Training to Fatigue Results in Muscle Hypertrophy Similar to High-Load Bench Press Training. *Int J Clin Med* 2013;04:114–21. doi:10.4236/ijcm.2013.42022.
- [38] Schoenfeld BJ, Wilson JM, Lowery RP, Krieger JW. Muscular adaptations in low- versus high-load resistance training: A meta-analysis. *Eur J Sport Sci* 2016;16:1–10. doi:10.1080/17461391.2014.989922.
- [39] Schoenfeld BJ, Contreras B, Willardson JM, Fontana F, Tiriyaki-Sonmez G. Muscle activation during low- versus high-load resistance training in well-trained men. *Eur J Appl Physiol* 2014;114:2491–7. doi:10.1007/s00421-014-2976-9.
- [40] Husmann F, Mittlmeier T, Bruhn S, Zschorlich V, Behrens M. Impact of Blood Flow Restriction Exercise on Muscle Fatigue Development and Recovery. *Med Sci Sport Exerc* 2017;50:1. doi:10.1249/MSS.0000000000001475.
- [41] Hughes L, Paton B, Rosenblatt B, Gissane C, Patterson SD. Blood flow restriction training in clinical musculoskeletal rehabilitation: A systematic review and meta-analysis. *Br J Sports Med* 2017;51:1003–11. doi:10.1136/bjsports-2016-097071.
- [42] Hughes L, Rosenblatt B, Haddad F, Gissane C, McCarthy D, Clarke T, et al. Comparing the Effectiveness of Blood Flow Restriction and Traditional Heavy Load Resistance Training in the Post-Surgery Rehabilitation of Anterior Cruciate Ligament Reconstruction Patients: A UK National Health Service Randomised Controlled Trial. *Sport Med* 2019;0. doi:10.1007/s40279-019-01137-2.
- [43] Korakakis V, Whiteley R, Giakas G. Low load resistance training with blood flow restriction decreases anterior knee pain more than resistance training alone. A pilot randomised controlled trial. *Phys Ther Sport* 2018;34:121–8. doi:10.1016/j.ptsp.2018.09.007.
- [44] Korakakis V, Whiteley R, Epameinontidis K. Blood Flow Restriction induces hypoalgesia in recreationally active adult male anterior knee pain patients allowing therapeutic exercise loading. *Phys Ther Sport* 2018;32:235–43. doi:10.1016/j.ptsp.2018.05.021.
- [45] Rodrigues R, Ferraz RB, Kurimori CO, Guedes LK, Lima FR, de Sá-Pinto AL, et al. Low-load resistance

- training with blood flow restriction increases muscle function, mass and functionality in women with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2019;doi: 10.1002/acr.23911. doi:10.1002/acr.23911.
- [46] Hughes L, Patterson SD, Haddad F, Rosenblatt B, Gissane C, McCarthy D, et al. Examination of the comfort and pain experienced with blood flow restriction training during post-surgery rehabilitation of anterior cruciate ligament reconstruction patients: A UK National Health Service trial. *Phys Ther Sport* 2019;39:90–8. doi:10.1016/j.pts.2019.06.014.
- [47] Jones MD, Booth J, Taylor JL, Barry BK. Aerobic training increases pain tolerance in healthy individuals. *Med Sci Sports Exerc* 2014;48:1640–7. doi:10.1249/MSS.0000000000000273.
- [48] Jones MD, Taylor JL, Barry BK. Occlusion of blood flow attenuates exercise-induced hypoalgesia in the occluded limb of healthy adults. *J Appl Physiol* 2017;122:1284–91. doi:10.1152/jap.01004.2016.
- [49] Hohmann AG, Suplita RL. Endocannabinoid Mechanisms of Pain Modulation. *AAPS J* 2006;8:693–708. doi:10.1208/aapsj080479.
- [50] Stagg NJ, Mata HP, Ibrahim MM, Henriksen EJ, Porreca F, Vanderah TW, et al. Regular Exercise Reverses Sensory Hypersensitivity in a Rat Neuropathic Pain Model. *Anesthesiology* 2011;114:940–8. doi:10.1097/ALN.0b013e318210f880.
- [51] Walker JM, Homann AG. Cannabinoid mechanisms of pain suppression. *Handb Exp Pharmacol* 2005;168:509–54.
- [52] Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A. Exercise activates the endocannabinoid system. *Cogn Neurosci Neurophysiol* 2003;2:2209–11. doi:10.1097/00001756-200312020-00015.
- [53] Koltyn KF, Umeda M. Exercise, Hypoalgesia and Blood Pressure. *Sport Med* 2006;36:207–14. doi:10.2165/00007256-200636030-00003.
- [54] Bruehl S, Chung OY. Interactions between the cardiovascular and pain regulatory systems : an updated review of mechanisms and possible alterations in chronic pain. *Neurosci Biobehav Rev* 2004;28:395–414. doi:10.1016/j.neubiorev.2004.06.004.
- [55] Ring C, Edwards L, Kavussanu M. Effects of isometric exercise on pain are mediated by blood pressure. *Biol Psychol* 2008;78:123–8. doi:10.1016/j.biopsycho.2008.01.008.
- [56] Koltyn KF, Trine MR, Stegner AJ, Tobar DA. Effect of isometric exercise on pain perception and blood pressure in men and women. *Med Sci Sport Exerc* 2001;33:282–90.
- [57] Tousignant-Laflamme Y, Rainville P, Marchand S. Establishing a Link Between Heart Rate and Pain in

- Healthy Subjects: A Gender Effect. *J Pain* 2005;6:341–7. doi:10.1016/j.jpain.2005.01.351.
- [58] Ellingson LD, Koltyn KF, Kim J, Cook DB. Does exercise induce hypoalgesia through conditioned pain modulation? *Psychophysiology* 2014;51:267–76. doi:10.1111/psyp.12168.
- [59] Lemley KJ, Hunter SK, Bement MKH. Conditioned Pain Modulation Predicts Exercise-Induced Hypoalgesia in Healthy Adults. *Med Sci Sport Exerc* 2014;47:176–84. doi:10.1249/MSS.0000000000000381.
- [60] Pollak KA, Swenson JD, Vanhaitsma TA, Hughen RW, Jo D, Light C, et al. Exogenously applied muscle metabolites synergistically evoke sensations of muscle fatigue and pain in human subjects. *Exp Physiol* 2014;2:368–80. doi:10.1113/expphysiol.2013.075812.
- [61] Stein C. The control of pain in peripheral tissue by opioids. *N Engl J Med* 1995;332:1685–90.
- [62] Miller RD. *Miller's Anesthesia*. 6th ed. Pennsylvania: Elsevier; 2005.
- [63] Sprouse-Blum A, Smith G, Sugai D, Don Parsa F. Understanding ndorphins and Their Importance in Pain Management. *Hawai'i Med J* 2010;69:70–1.
- [64] Kjaer M, Secher NH, Bach FW, Galbo H, Reeves DR, Mitchell JH. Hormonal, metabolic, and cardiovascular exercise in humans: influence of epidural responses to static anesthesia. *Am Physiol Soc* 1991;261:E214–20. doi:10.1152/ajpendo.1991.261.2.E214.
- [65] Haier RJ, Quaid K, Mills JC. Naloxone alters pain perception after jogging. *Psychiatry Res* 1981;5:231–2.
- [66] Janal MN, Colt EW, Clark WC, Glusman M. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain* 1984;19:13–25.
- [67] Marek P, Mogil JS, Sternberg WE, Panocka I. N-Methyl-o-aspartic acid (NMDA) receptor antagonist MK-801 blocks non-opioid stress-induced analgesia. II. Comparison across three swim-stress paradigms in selectively bred mice. *Brain Res* 1992;578:197–203.
- [68] Watkins BA. Molecular Aspects of Medicine Endocannabinoids, exercise, pain, and a path to health with aging. *Mol Aspects Med* 2018;64:68–78. doi:10.1016/j.mam.2018.10.001.
- [69] Starowicz K, Malek N, Przewlocka B. Cannabinoid receptors and pain. *WIREs Membr Transp Signal* 2013;2:121–32. doi:10.1002/wmts.83.
- [70] Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol* 2001;63:569–611.
- [71] Feurecker M, Hauer D, Toth R, Demetz F, Holzl J, Thiel M, et al. Effects of exercise stress on the endocannabinoid system in humans under field conditions. *Eur J Appl Physiol* 2012;112:2777–81.

doi:10.1007/s00421-011-2237-0.

- [72] Raichlen DA, Foster AD, Seillier A, Giuffrida A, Gerdeman GL. Exercise-induced endocannabinoid signaling is modulated by intensity. *Eur J Appl Physiol* 2013;113:869–75. doi:10.1007/s00421-012-2495-5.
- [73] Heyman E, Gamelin F, Goekint M, Piscitelli F, Roelands B, Leclair E, et al. Intense exercise increases circulating endocannabinoid and BDNF levels in humans - Possible implications for reward and depression. *Psychoneuroendocrinology* 2012;37:844–51. doi:10.1016/j.psyneuen.2011.09.017.
- [74] Hohmann AG, Herkenham M. Localization of central cannabinoid CB1 receptor messenger RNA in neuronal subpopulations of rat dorsal root ganglia: A double-label in situ hybridization study. *Neuroscience* 1999;90:923–31.
- [75] Randich A, Maixner W. Interactions between cardiovascular and pain regulatory systems. *Neurosci Biobehav Rev* 1984;8:343-367;
- [76] Lovick TA. Integrated activity of cardiovascular and pain regulatory systems: Role in adaptive behavioural responses. *Prog Neurobiol* 1993;40:631–44.
- [77] Ghione S. Hypertension-associated hypalgesia: Evidence in experimental animals and humans; pathological mechanisms; and potential clinical consequences. *Hypertension* 1996;28:494–504.
- [78] Friedman R, Murphy D, Persons W, McCaughran Jr. JA. Genetic predisposition to hypertension , elevated blood pressure and pain sensitivity : a functional analysis. *Behav Brain Res* 1984;12:75–9.
- [79] France CR, Suchowiecki S. Assessing supraspinal modulation of pain perception in individuals at risk for hypertension. *Psychophysiology* 2001;38:107–13.
- [80] Bruehl S, Yung O, Ward P, Johnson B, Mccubbin JA. The relationship between resting blood pressure and acute pain sensitivity in healthy normotensives and chronic back pain sufferers: the effects of opioid blockade. *Pain* 2002;100:191–201.
- [81] Myers C, Robinson ME, Riley JL, Sheffield D. Sex, Gender, and Blood Pressure: Contributions to Experimental Pain Report. *Psychosom Med* 2001;63:545–50.
- [82] Ghione S, Rosa C, Nuti M, Mezzasalma L, Giuliano G. Comparison of sensory and pain threshold in tooth pulp stimulation in normotensive man and essential hypertension. *J Hypertens Suppl* 1985;3:113–5.
- [83] Schobel HP, Handwerker HO, Schmieder RE, Heusser K, Dominiak P, Luft FC. Effects of naloxone on hemodynamic and sympathetic nerve responses to pain in normotensive vs. borderline hypertensive men. *J Auton Nerv Syst* 1998;69:49–55.

- [84] Zamir M, Maixner W. The relationship between cardiovascular and pain regulatory systems. *Ann N Y Acad Sci* 1986;467:371–84.
- [85] Droste C, Kardos A, Brody S, Greenlee MW, Roskamm H, Rau H. Baroreceptor stimulation: and sensory thresholds Pain perception. *Biol Psychol* 1994;37:101–13.
- [86] Rau H, Elbert T. Psychophysiology of arterial baroreceptors and the etiology of hypertension. *Biol Psychol* 2001;57:179–201.
- [87] Chitour D, Dickenson A., Le Bars D. Pharmacological evidence for the involvement of serotonergic mechanisms in diffuse noxious inhibitory controls (DNIC). *Brain Res* 1982;236:329–37.
- [88] Le Bars D, Willer J. Diffuse noxious inhibitory controls (DNIC). In: Basbaum AI, Bushnell MC, editors. *Sci. Pain.*, Oxford (UK): Elsevier; 2009, p. 763–73.
- [89] Willer J., De Broucker T, Le Bars D. Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. *J Neurophysiol* 1989;62:1028–38.
- [90] Oono Y, Wang K, Svensson P, Arendt-Nielsen L. Conditioned pain modulation evoked by different intensities of mechanical stimuli applied to the craniofacial region in healthy men and women. *J Orofac Pain* 2011;25:364–75.
- [91] Fingleton C, Smart KM, Doody CM. Exercise-induced Hypoalgesia in People With Knee Osteoarthritis With Normal and Abnormal Conditioned Pain Modulation. *Clin J Pain* 2017;33:395–404. doi:10.1097/AJP.0000000000000418.
- [92] Bangsbo J, Krstrup P, Gonzalez-Alonso J, Saltin B. ATP production and efficiency of human skeletal muscle during intense exercise: effect of previous exercise. *Am J Physiol - Endocrinol Metab* 2001;280:956–64.
- [93] Mohr M, Krstrup P, Nielsen JJ, Nybo L, Rasmussen MK, Juel C, et al. Effect of two different intense training regimens on skeletal muscle ion transport proteins and fatigue development. *Am J Physiol - Regul Integr Comp Physiol* 2007;292:1594–602. doi:10.1152/ajpregu.00251.2006.
- [94] Light AR, Huguen RW, Zhang J, Rainier J, Liu Z, Lee J, et al. Dorsal Root Ganglion Neurons Innervating Skeletal Muscle Respond to Physiological Combinations of Protons , ATP , and Lactate Mediated by ASIC , P2X , and TRPV1 Dorsal Root Ganglion Neurons Innervating Skeletal Muscle Respond to Physiological Combinations. *J Neurophysiol* 2014;100:1184–201. doi:10.1152/jn.01344.2007.
- [95] Khan MH, Sinoway LI. Muscle Reflex Control of Sympathetic Nerve Activity in Heart Failure: The Role of Exercise Conditioning. *Heart Fail Rev* 2000;5:87–100.

- [96] Secher NH, Amann M. Human investigations into the exercise pressor reflex. *Exp Physiol* 2012;97:59–69. doi:10.1113/expphysiol.2011.057679.
- [97] Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain* 1996;64:415–23.
- [98] Kosek E, Ekholm J. Modulation of pressure pain thresholds during and following isometric contraction. *Pain* 1995;61:481–6.
- [99] Paalasmaa P, Kempainen P, Pertovaara A. Modulation of skin sensitivity by dynamic and isometric exercise in man. *Eur J Appl Physiol Occup Physiol* 1991;62:279–85.
- [100] Feine JS, Chapman FE, Lund JP, Duncan GH, Bushnell MC. The perception of painful and nonpainful stimuli during voluntary motor activity in man. *Somatosens Mot Res* 1990;7:113–4.
- [101] Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain* 2005;118:176–84. doi:10.1016/j.pain.2005.08.007.
- [102] Fallentin N, Jørgensen K, Simonsen EB. Motor unit recruitment during prolonged isometric contractions. *Eur J Appl Physiol Occup Physiol* 1993;67:335–41.
- [103] Hughes L, Paton B, Haddad F, Rosenblatt B, Gissane C, Patterson SD. Comparison of the acute perceptual and blood pressure response to heavy load and light load blood flow restriction resistance exercise in anterior cruciate ligament reconstruction patients and non-injured populations. *Phys Ther Sport* 2018;33:54–61. doi:https://doi.org/10.1016/j.ptsp.2018.07.002.
- [104] Suga T, Okita K, Morita N, Yokota T, Hirabayashi K, Horiuchi M, et al. Intramuscular metabolism during low-intensity resistance exercise with blood flow restriction. *J Appl Physiol* 2009;106:1119–24. doi:10.1152/jappphysiol.90368.2008.
- [105] Victor RG, Seals DR. Reflex stimulation of sympathetic outflow during rhythmic exercise in humans. *Am J Physiol* 1989;257:2017–24. doi:10.1152/ajpheart.1989.257.6.H2017.
- [106] Gosselink KL, Grindeland RE, Roy RR, Zhong H, Bigbee AJ, Grossman EJ, et al. Skeletal muscle afferent regulation of bioassayable growth hormone in the rat pituitary. *J Appl Physiol* 1985;84:1425–30.
- [107] Jessee MB, Dankel SJ, Buckner SL, Mouser JG, Mattocks KT, Loenneke JP. The Cardiovascular and Perceptual Response to Very Low Load Blood Flow Restricted Exercise Authors. *Int J Sports Med* 2017;38:597–603. doi:10.1055/s-0043-109555.
- [108] Loenneke JP, Kim D, Fahs CA, Thiebaud RS, Abe T, Larson RD, et al. The effects of resistance exercise

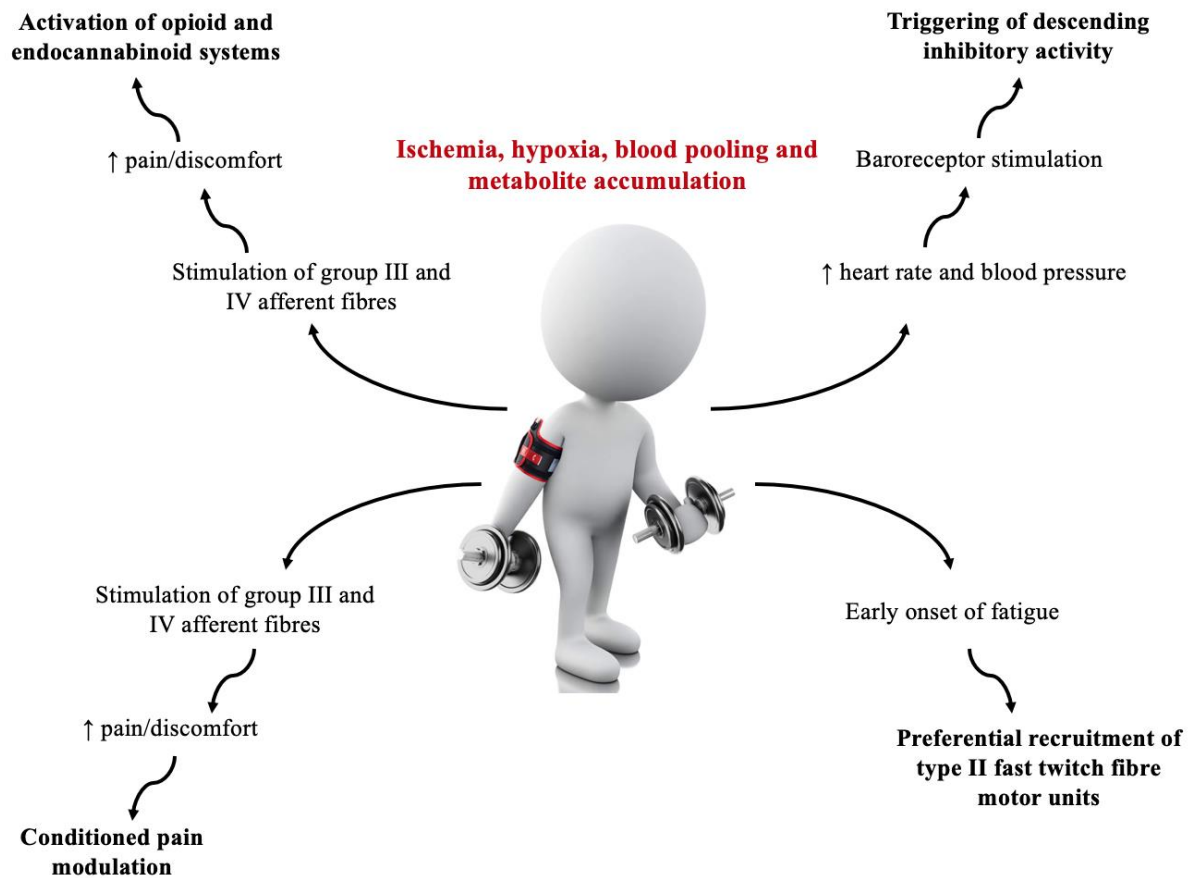


- with and without different degrees of blood-flow restriction on perceptual responses. *J Sports Sci* 2015;33:1472–9. doi:10.1080/02640414.2014.992036.
- [109] Takarada Y, Nakamura Y, Aruga S, Onda T, Miyazaki S, Ishii N, et al. Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion restriction Rapid increase in plasma growth hormone after low-intensity resistance exercise with vascular occlusion. *J Appl Physiol* 2000;88:61–5.
- [110] Loenneke JP, Balapur A, Thrower AD, Barnes JT, Pujol TJ. The perceptual responses to occluded exercise. *Int J Sports Med* 2011;32:181–4. doi:10.1055/s-0030-1268472.
- [111] Hollander DB, Reeves G V., Clavier JD, Francois MR, Thomas C, Kraemer RR. Partial occlusion during resistance exercise alters effort sense and pain. *J Strength Cond Res* 2010;24:235–43. doi:10.1519/JSC.0b013e3181c7badf.
- [112] Martín-Hernández J, Ruiz-Aguado J, Herrero AJ, Loenneke JP, Aagaard P, Cristi-Montero C, et al. Adaptation of perceptual responses to low-load blood flow restriction training. *J Strength Cond Res* 2016;31:765–72. doi:10.1519/JSC.0000000000001478.
- [113] Pereira FEC, Mello IL, Pimenta FHDOM, Costa DM, Wong DVT, Fernandes CR, et al. A clinical experimental model to evaluate analgesic effect of remote ischemic preconditioning in acute postoperative pain. *Pain Res Treat* 2016;2016:1–6. doi:10.1155/2016/5093870.
- [114] Memtsoudis SG, Stundner O, Yoo D, Gonzalez Della Valle A, Boettner F, Bombardieri AM, et al. Does limb preconditioning reduce pain after total knee arthroplasty? A randomized, double-blind study. *Clin Orthop Relat Res* 2014;472:1467–74. doi:10.1007/s11999-013-3106-4.
- [115] Page W, Swan R, Patterson SD. The effect of intermittent lower limb occlusion on recovery following exercise-induced muscle damage: A randomized controlled trial. *J Sci Med Sport* 2017;20:729–33. doi:10.1016/j.jsams.2016.11.015.
- [116] Henneman E, Somjen G, Carpenter DO. Excitability and Inhibitibility of Motoneurons of Different Sizes. *J Neurophysiol* 1965;28:599–620. doi:10.1152/jn.1965.28.3.599.
- [117] Pearson SJ, Hussain SR. A Review on the Mechanisms of Blood-Flow Restriction Resistance Training-Induced Muscle Hypertrophy. *Sport Med* 2015;45:187–200. doi:10.1007/s40279-014-0264-9.
- [118] Wernbom M, Augustsson J, Raastad T. Ischemic strength training: A low-load alternative to heavy resistance exercise? *Scand J Med Sci Sport* 2008;18:401–16. doi:10.1111/j.1600-0838.2008.00788.x.
- [119] Fatela P, Reis JF, Mendonca G V., Avela J, Mil-Homens P. Acute effects of exercise under different levels

- of blood-flow restriction on muscle activation and fatigue. *Eur J Appl Physiol* 2016;116:985–95. doi:10.1007/s00421-016-3359-1.
- [120] Lauver JD, Cayot TE, Rotarius T, Scheuermann BW. The effect of eccentric exercise with blood flow restriction on neuromuscular activation, microvascular oxygenation, and the repeated bout effect. *Eur J Appl Physiol* 2017;117:1005–15. doi:10.1007/s00421-017-3589-x.
- [121] Yasuda T, Brechue WF, Fujita T, Sato Y, Abe T. Muscle activation during low-intensity muscle contractions with varying levels of external limb compression. *J Sport Sci Med* 2008;7:467–74.
- [122] Yasuda T, Brechue W, Fujita T, Shirakawa J, Sato Y, Abe T. Muscle activation during low-intensity muscle contractions with restricted blood flow. *J Sports Sci* 2009;27:479–89. doi:10.1080/02640410802626567.
- [123] Moritani T, Sherman WM, Shibata M, Matsumoto T, Shinohara M. Oxygen availability and motor unit activity in humans. *Eur J Appl Physiol Occup Physiol* 1992;64:552–6. doi:10.1007/BF00843767.
- [124] Yasuda T, Fujita T, Miyagi Y, Kubota Y, Sato Y, Nakajima T, et al. Electromyographic responses of arm and chest muscle during bench press exercise with and without KAATSU. *Int J KAATSU Train Res* 2006;2:15–8. doi:10.3806/ijktr.2.15.
- [125] Takano H, Morita T, Iida H, ichi Asada K, Kato M, Uno K, et al. Hemodynamic and hormonal responses to a short-term low-intensity resistance exercise with the reduction of muscle blood flow. *Eur J Appl Physiol* 2005;95:65–73. doi:10.1007/s00421-005-1389-1.
- [126] Takano H, Morita T, Iida H, Kato M, Uno K, Hirose K, et al. Effects of low-intensity “KAATSU” resistance exercise on hemodynamic and growth hormone responses. *Int J KAATSU Train Res* 2005;1:13–8. doi:10.3806/ijktr.1.13.
- [127] Sakamaki M, Fujita S, Sato Y, Bemben MG, Abe T. Blood pressure response to slow walking combined with KAATSU in the elderly. *Int J KAATSU Train Res* 2008;4:17–20. doi:10.3806/ijktr.4.17.
- [128] Poton R, Polito MD. Hemodynamic response to resistance exercise with and without blood flow restriction in healthy subjects. *Clin Physiol Funct Imaging* 2016;36:231–6. doi:10.1111/cpf.12218.
- [129] Pinto RR, Karabulut M, Poton R, Polito MD. Acute resistance exercise with blood flow restriction in elderly hypertensive women: Haemodynamic, rating of perceived exertion and blood lactate. *Clin Physiol Funct Imaging* 2016:1–8. doi:10.1111/cpf.12376.
- [130] 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 - Hear Circ Physiol* 2015;309:1440–52.

doi:10.1152/ajpheart.00208.2015.

- [131] Mouser JG, Mattocks KT, Buckner SL, Dankel SJ, Jessee MB, Bell ZW, et al. High-pressure blood flow restriction with very low load resistance training results in peripheral vascular adaptations similar to heavy resistance training. *Physiol Meas* 2019;40:1–20. doi:10.1088/1361-6579/ab0d2a.
- [132] Mattocks KT, Jessee M, Counts BR, Buckner SL, Grant Mouser J, Dankel SJ, et al. The effects of upper body exercise across different levels of blood flow restriction on arterial occlusion pressure and perceptual responses. *Physiol Behav* 2017;171:181–6. doi:10.1016/j.physbeh.2017.01.015.
- [133] Patterson SD, Hughes L, Warmington S, Burr J, Scott BR, Owens J, et al. Blood Flow Restriction Exercise Position Stand: Considerations of Methodology, Application, and Safety. *Front Physiol* 2019;10:1–15. doi:10.3389/fphys.2019.00533.



**Figure 1.** Overview of the possible mechanisms driving exercise-induced hypoalgesia with low intensity blood flow restriction exercise