

# Metabolic Stress and Blood Flow Restriction Training as Interventions for Skeletal Muscle Atrophy following Musculoskeletal Injury

Michael Bower<sup>1</sup>

<sup>1</sup>University of Leeds.

## ABSTRACT

Skeletal muscle loss poses significant health issues to both the general clinical population, but also athletes recovering from musculoskeletal (MSK) injury. Resistance training is known to induce skeletal muscle hypertrophy (SMH) and whilst 70% of an individual's one repetition maximum (1RM) is advantageous to elicit such changes, increasing evidence suggest that this is not compulsory. It is not always feasible for the abovementioned populations to be exposed to high degrees of mechanical force due to rheumatic limitations and thus, targeting metabolic stress as a stimulus for skeletal muscle hypertrophy may be more favourable than that of mechanical tension. Blood Flow Restriction (BFR) training achieves potent levels of metabolic stress by occluding venous out-flow whilst sustaining arterial in-flow to the working muscle, resulting in a pooling of anaerobic metabolites. As a result, resistance training loads as low as 20% 1RM are capable of eliciting hypertrophic effects equivalent to training at heavier loads, and such adaptations have been attributed to both endocrine and intramuscular mechanisms. Safe administration of BFR is paramount, especially when prescribing to post-surgical individuals. As such, the coach or clinician in question must take careful consideration regarding pressure application, rest periods and various patient characteristics such as post-surgical timeframe and overall health status.

## INTRODUCTION

Skeletal muscle atrophy poses significant problems to the health and quality of life of many individuals

including both general and athletic populations. From an MSK perspective, excessive atrophy can have implications on an individual's rehabilitation capacity following injury (Wall et al., 2014). For example, with over 10% of all Olympians facing MSK injury based on data from the last three events (Vasta et al., 2018), it is crucial that coaches and clinicians involved in high-level sport are understanding of the impacts this has on an individual.

Muscle loss typically occurs in response to chronic periods of immobility such as post-surgical or post-injury (Parry and Puthuchear, 2015). This is due to skeletal muscle displaying high levels of plasticity, whereby it responds and adapts to both increased and decreased usage (Aguilar-Agon et al., 2019). This is a necessary requirement for muscle homeostasis, whereby the body maintains its internal regularity through a delicate balance between synthesis and degradation of cellular proteins, complementary to the environment it faces (Scicchitano et al., 2018).

In addition to MSK injury, it is the responsibility of a coach or clinician to consider the individual's age, and what effect that may have on their ability to sustain and enhance muscle mass. More specifically, age-related muscle loss known as sarcopenia can begin as early as the fourth decade of life (Walston, 2014), and is characterised by disruptions to the complex interactions that exist between anabolic and catabolic signalling pathways. Additionally, muscle wastage caused by sarcopenia often onsets further MSK issues amongst the aging population, including those of aging athletes (Siparsky et al., 2014).

Sarcopenia occurs due to disruptions to various anabolic signalling pathways which regulate skeletal

muscle homeostasis. As such, disproportionately high levels of catabolic signalling will result in the wastage and loss of function of skeletal muscle. Seeing as sarcopenia is an issue frequently faced by aging individuals, hypertrophy training should be a major focal point within their weekly physical activity or, in the case of aging athletes, their training plan. This may reduce the effects of sarcopenia and decrease the likelihood of subsequent injury. Such a concept is supported by Yeung et al. (2019) who described sarcopenia as being a modifiable risk factor for falls amongst older adults, and found a positive association of sarcopenia with falls and fractures. Furthermore, a bidirectional causal pathway was described between sarcopenia, and falls and fractures. Not only does sarcopenia increase the likelihood of falls and fractures as a secondary complication, but falls and fractures may in fact accelerate the onset of sarcopenia via reduction in physical activity and mobility driven by a fear of re-falling and hospitalisation.

Healthcare professionals are therefore posed with a dilemma: Whilst it is clear amongst the literature that falls, fractures and sarcopenia are interlinked, those most vulnerable to such incidents, as well as MSK recoverees, are unlikely to be able to expose themselves to the threshold of mechanical tension required to elicit muscular adaptation. As such, the stimulus of metabolic stress presents itself as a valid option for the avoidance of skeletal muscle loss and prevention of secondary health complications.

As highlighted above, skeletal muscle atrophy is a

significant issue facing a variety of demographics within a given population and as such, gaining an understanding of muscle plasticity and strategies to prevent its loss in a safe and practical manner is crucial for the avoidance of further health complications.

## SIGNALLING PATHWAYS PERTINENT TO HYPERTROPHY

Highlighted in table 1 is a summary of various signalling pathways which regulate skeletal muscle. Whilst it is arguably not essential for a coach or clinician to understand these pathways in great depth, it is of value for such professionals to consider them in order to develop a rounded knowledge of skeletal muscle physiology. These pathways are mediators of the effects of metabolic stress and BFR training which will be discussed.

In the example of sarcopenia in middle age to mature athletes, upregulation of the FoxO1 pathway suppresses mTOR activation, altering the tightly regulated balance between anabolic and catabolic signalling (Ziaaldini et al., 2017).

Despite this, physiotherapists and coaches must bridge the gap between research findings and applications for treatment, which are both effective and practical for the athlete. For example, the stimuli of mechanical tension, muscle damage and metabolic stress are widely accepted as primary drivers of SMH (Schoenfeld, 2013). However, MSK

**Table 1.** Four common signalling pathways involved in the anabolic/catabolic balance of skeletal muscle.

Pathway	Anabolic/ Catabolic	Notes
<b>mTOR</b> (Mammalian Target of Rapamycin)	Anabolic	Consists of both mTORC1 and mTORC2 complexes. Considered to be the master regulator of cellular growth and proliferation through positive control over protein synthesis, and also downregulates catabolic processes such as autophagy (Laplanche and Sabatini, 2009).
<b>FOXO</b> (Forkhead Box O)	Catabolic	Activity is increased in response to various catabolic stimuli such as nutritional deficiencies, inactivity and disease (Senf et al., 2010).
<b>MAPK</b> (Mitogen-Activated Protein Kinase)	Anabolic	Activation of this pathway through exercise, muscle contraction and stress results in the release of substrates which promote transcriptional factors involved in protein synthesis (Williamson et al., 2003).
<b>P13K/AKT</b> (Phosphatidylinosi- tol 3-kinase)	Both	Acts as an umbrella pathway, which governs numerous downstream effects. P13K phosphorylates AKT which in turn activates one of numerous pathways such as FOXO or mTOR. The appropriate target pathway is dependent on environmental conditions at the time (Hemmings and Restuccia, 2012). Also stimulates Nitric Oxide release, which is beneficial for inducing hyperaemia and osmosensor activation, as discussed in a latter section (Chen et al., 2015).

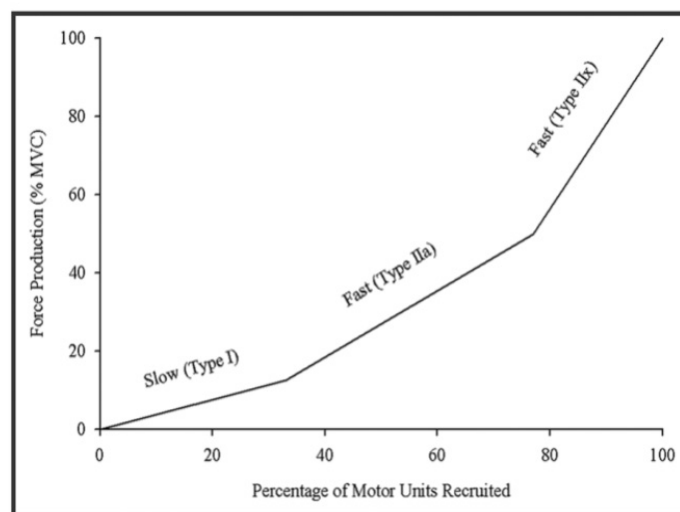
injury recoverees may find themselves unable to apply high levels of mechanical tension due to rheumatic limitations. Therefore, metabolic stress may be the most practical stimulus to apply not only to prevent excessive muscle loss during recovery stages, but possibly enhance it to a clinically optimal level.

## BLOOD FLOW RESTRICTION TRAINING

One effective modality through which substantial levels of exercise-induced metabolic stress can be achieved is Blood Flow Restriction training (BFR). BFR maintains arterial inflow whilst restricting venous outflow, thus resulting in a pooling of anaerobic metabolites in and around the muscle (Scott et al., 2014). Such metabolites include lactate, Hydrogen (H<sup>+</sup>) ions and inorganic phosphate (Pi), and these are key stimuli which initiate a cascade of responses which ultimately lead to increased protein accretion and increases in muscle size (Schliess et al., 2006).

BFR may prove effective at stimulating hypertrophy at low loads, whilst preserving rheumatic integrity (Hughes et al., 2018). Studies show that BFR training at 30% 1RM produces similar improvements in muscle size as heavy-load training, in subjects recovering from Anterior Cruciate Ligament reconstruction surgery (Hughes et al., 2019). However, other research suggests that mechanical tension still remains the most significant of hypertrophic stimuli, and whilst standard low-intensity training (without BFR) may have minor benefits for enhancing SMH, it is drastically less effective than heavy-load training at 70% 1RM (Hughes et al., 2019). This raises questions regarding the legitimacy of metabolic stress as a means to induce SMH. However, metabolic stress combined with BFR is thought to enhance SMH partly through increases in mechanical tension. For example, one mechanism through which metabolic stress induces SMH involves disruption of what is known as the Henneman Size Principle of Voluntary Motor Unit Recruitment, which involves the progressive increase in fibre recruitment as training intensity increases in order to sustain muscular contraction. At low intensities, initial recruitment of small, slow-twitch fibres occurs which progressively incorporates fast twitch IIa and IIx fibres as the stimulus increases (Gregory and Bickel, 2005).

**Figure 1.** The orderly recruitment of motor units during voluntary activation of skeletal muscle – known as the Size Principle (Gregory and Bickel, 2005, p.360).



Metabolic stress disrupts this gradually progressive recruitment of motor units and demands a higher proportion of total fibre recruitment at a lower load, thus increasing activation of type II fibres. This suggests that metabolic stress may induce SMH indirectly through increases in mechanical tension. Despite this, Mitchell et al. (2012) found similar effects in SMH between individuals performing volume-matched resistance training at 30% versus 80% 1RM, following a 10-week training programme for men aged 21 years ( $\pm 1$  year). This indicates that mechanical tension may be less significant as a stimulus for SMH than once thought, and that as long as metabolite-induced fatigue is reached, equivalent increases in hypertrophy can be achieved. This raises the question as to whether metabolic stress receives enough credit as a modulator of SMH.

## PREVENTION OF SECONDARY INJURY/ RE-INJURY

Additionally, BFR may serve as a preventative means in order to avoid secondary injury, by halting progressive muscle loss which consistently precedes poor clinical outcomes (DePhillipo et al., 2018). Research has highlighted a significant correlation between reduction in quadriceps size and strength, and onset of knee osteoarthritis (Alnahdi et al., 2012). Therefore, assessment of muscular atrophy should take place and subsequent administration of BFR by a coach or clinician may slow the rate of muscle loss, attenuating further rheumatic issues such as osteoarthritis. However, this study lacks population validity due to knee osteoarthritis being predominant amongst older adults as opposed to

the young, uninjured and competitive population. Therefore, Aroen et al. (2004) found that following Achilles tendon injury in athletes under the age of 30, the risk of reinjury is significantly greater due to disuse atrophy. Furthermore, resultant decline in activity levels following initial injury caused atrophy in the contralateral limb, also exposing it to subsequent injury. This indicates that in order to avoid atrophy of both contralateral and injured limbs, rapid recovery time is paramount. Kraemer et al. (2009) suggest that recovery time is mediated through rapid reincorporation of resistance training and thus, whilst rheumatic limitations may render the athlete unable to apply high levels of mechanical tension, swift administration of BFR to attenuate the onset of catabolic signalling would be beneficial to both injured and contralateral limbs.

## MECHANISMS OF SMH

As mentioned, the degree of muscle preservation is regulated by a complex interaction between anabolic and catabolic signalling pathways, and the basis of these pathways is typically either an upregulation or downregulation of muscle protein synthesis/breakdown (MPS/MPB) (McCarthy and Esser, 2010). Highlighted below are a list of various mechanisms which may account for the hypertrophy-inducing effects of BFR-mediated metabolic stress.

## APPLICATION OF BFR

Patterson et al. (2019) suggest that practitioners are

unclear on how to administer BFR in line with current research-informed standards. As such, coaches and clinicians would benefit from globalised, evidence-based guidelines on safe application.

It is widely accepted that BFR cuffs should be placed on the proximal portion of the limb prior to inflation to the desired pressure (Weatherholt et al., 2019). However, findings regarding optimal pressure application are inconsistent. Loenneke et al. (2013) suggested that appropriate pressure identification should be calculated relative to the patient's systolic blood pressure (1.2-1.5x). However, Ilett et al. (2019) found that pressure as a percentage of total limb occlusion pressure (LOP) is the safest means to apply BFR, with a minimum effective dose ranging between 60-80% LOP, determined by Doppler ultrasound. This method is arguably more suitable and addresses the issue that applying pressures as a percentage of systolic blood pressure does not account for subsequent increases in blood pressure following commencement of exercise, resulting in insufficient occlusion. Additionally, utilising percentage LOP means that sub-maximal pressures can be progressively increased similar to progressive overload of resistance training, thus sustaining upregulation of various anabolic signalling pathways such as mTOR. Whilst the practicality of accessing a Doppler ultrasound may be questioned, it remains the responsibility of the coach or clinician to ensure safe and proper usage for this training modality. As such, investment into both blood pressure cuffs and transportable Doppler

**Table 2.** Mechanisms through which metabolic stress induces SMH

Mechanism	Description
<b>Muscle Fibre Recruit-ment</b>	Alterations made to the Henneman Size Principle of Voluntary Motor Unit Recruitment, whereby higher-threshold motor units (predominantly Type-2 fibres) are recruited to a lower load (Loenneke et al., 2011)
<b>Hormone Production</b>	Upregulation of anabolic hormones such as Growth Hormone and IGF-1 in response to metabolic stress causes an increase in downstream accretion of muscle proteins and decreased proteolysis (de Freitas et al., 2017)
<b>Local Myokines</b>	Resistance training-induced metabolic stress may cause an upregulation of anabolic myokines and/or downregulation of catabolic myokines (Schoenfeld, 2013)
<b>Reactive Oxygen Species (ROS)</b>	Acute ROS build-up signals of SMH via protein synthesis upregulation, which is triggered via MAPK activation (Dutra et al., 2019)
<b>Oedema</b>	Lactic acid accumulation causes alterations in intramuscular water balance due to osmotic potential changes. This causes movement of water from circulation into the muscle, resulting in cell swelling. This cell swelling (known as reactive hyperaemia) compromises the cell membrane's integrity, resulting in upregulation of protein synthesis via mTOR and MAPK pathways in order to accommodate for this size increase (Schoenfeld, 2013).

ultrasound devices is recommended.

Research is conclusive that rest periods lasting longer than 60 seconds are ineffective at sustaining a metabolically stressful environment; no more effective than regular low-load training (Loenneke et al., 2010). It is suggested that the 30-60 second sensitive timeframe relates to phosphocreatine and pH restoration and thus elongated rest periods resume the normal contractility of muscle fibres (Okita et al., 2019).

## CONSIDERATIONS AND DISCUSSION

Various risk factors apply particularly to mature or orthopaedic post-operative athletes. For example, Vascular Thromboembolism (VTE) is increased nearly 100-fold for post-surgical patients in the first six weeks following surgery, and this must be considered alongside hereditary thrombophilia (V-Leiden mutation or prothrombin deficiencies) which should be enquired about prior to administration of BFR (Bond et al., 2019).

Amongst post-surgical athletes, infection and immobility are highly relevant risk factors, possibly exacerbated by BFR. Tabata et al. (2016) highlighted that BFR increases risk of rhabdomyolysis amongst inactive patients, and the secretion of muscular contents into the circulation can lead to kidney injury and increased risk of infection (Vandijck et al., 2007). Therefore, it could be argued that BFR is unsuitable as a method of rehabilitation amongst bed-bound patients, whose immobility and increased risk of infection magnify the risks of rhabdomyolysis. Having said that, reluctance of patients to engage in a traditional rehabilitative training program may be overcome with low-load exercise and BFR, and the benefits of mobilisation could outweigh the associated risks. Thus, granted appropriate application and sufficient medical background checks, the effects of BFR may actually decrease VTE risk by reducing haemostasis and restoring adequate blood flow to the injured limb. This is supported by Madarama et al. (2012) who found that traditional heavy-loaded exercise (>70% 1RM) causes alterations in pro-haemostatic markers. This was not present in low resistance BFR, indicating that it would be a safe training modality for patients with compromised vascular health. However, these findings may lack validity as the participants were not of the athletic demographic. In fact, several participants in this study were treated with stent

implants in order to improve blood flow. Whilst findings are useful for insight into BFR use in cardiac patients, artificial expansion of vessels distorts the true effects of BFR on haemostasis. Therefore, haemostatic responses to BFR versus heavy-load training in a healthy or athletic sample is a matter for future research.

Finally, endothelial damage is of concern due to highly invasive and aberrant procedures during certain MSK surgeries. This is justified whereby total hip arthroplasty sees higher numbers of VTE than the less invasive knee ligament reconstruction (Bond et al., 2019). Therefore, due to the risk of vascular reinjury and upregulation in procoagulant activity, BFR should be approached with caution. However, whilst this may be the case for post-surgical patients, BFR in healthy samples have beneficial effects on vascularity. Evans et al. (2010) found that following a 4-week training plan for the gastrocnemius, the occluded leg displayed increased calf filtration capacity (an indicator of capillarisation) by 26%. This indicates that BFR use in healthy populations actually has beneficial vascular effects. Despite this, BFR had no effect on fatiguability of the gastrocnemius which implies that despite enhanced vascularity, increases to oxidative capacity did not occur. Thus, future research using matched pairs design could investigate differences in fatiguability following BFR-aerobic protocols of differing intensities.

## LIMITATIONS

Limitations of BFR include the cardiovascular risks posed even to athletic populations. During normal exercise without BFR, peripheral resistance lowers in concert with increased cardiac output. However, MacDougall et al. (1992) found that due to the inability for sufficient vasodilation during BFR, blood pressure values as high as 480/250mmHg, and a doubling mean arterial pressure of 114-212mmHg were observed, having serious implications regarding possible onset of major cardiac events amongst vulnerable individuals (Yu et al., 2016).

It should be noted however, that traditional resistance exercise also displays drastic increases in blood pressure. Phillips and Donofrio (2009) describe sympathetically-driven spikes in blood pressure following Valsalva manoeuvre; a technique often employed during heavy lifting in order to increase intrathoracic and abdominal pressure, heighten axial rigidity, and subsequently enhance lifting

capacity. Therefore, it appears that blood pressure fluctuations are pertinent to both traditional and BFR resistance training, and as such individuals who are cardiac compromised should consult a medical professional prior to engagement in such activity.

Additionally, the research of Yu et al. (2016) fails to provide detailed explanation for this cardiovascular response. Therefore, a concept put forward by Spranger et al. (2015) suggests that BFR activates the Exercise Pressor Reflex (EPR) through targeting both the metaboreflexive (lactate accumulation) and mechanoreflexive (pressure application) subcomponents. EPR contributes to autonomic cardiovascular responses and thus, with its upregulation comes greater sympathetic drive and a heightened risk of adverse cardiac events.

Finally, despite the convincing argument supporting this form of training, the underlying mechanisms of metabolic stress and BFR still appear under discussion. A study by Gundermann et al (2012) found that reactive hyperaemia occurring subsequent to BFR training is not responsible for stimulating MPS. When participants underwent BFR training as a control group, or injection with sodium nitroprusside (vasodilator to mimic reactive hyperaemia), the BFR control experienced a 49% increase of mixed-muscle fractional synthetic rate, compared to no change in the injected experimental group. This implies that whilst BFR does stimulate MPS, reactive hyperaemia is not a primary mechanism through which this occurs. Therefore, future research should address this and determine a more robust understanding on the precise mechanisms involved in metabolic stress inducing hypertrophy.

## CONCLUSION

The detrimental effects of skeletal muscle atrophy amongst athletes can be targeted and possibly overcome by the utilisation of metabolic stress as a mediator of SMH. This enables swift return to physical activity following MSK injury or surgery, which is known to be a major determinant of clinical progression and return-to-play. BFR training is an effective modality through which resistance exercise-induced metabolic stress can be achieved, and as such alleviates the requirement for high levels of mechanical tension to be applied to the recovering limb or joint in question. Various precautions should be made regarding usage of BFR, and proper training should be carried out prior to its application in the coaching or clinical setting.

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