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SAFETY CONSIDERATIONS WITH BLOOD FLOW RESTRICTED RESISTANCE TRAINING

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ABSTRACT

Blood flow restricted resistance (BFRR) training with pneumatic tourniquet has been suggested as an alternative for conventional weight training due to the proven benefits for muscle strength and hypertrophy using relatively low resistance, hence reducing the mechanical stress across a joint. As such, it has become an important part of rehabilitation programs used in either injured or operated athletes. Despite a general consensus on effectiveness of BFRR training for muscle conditioning, there are several uncertainties regarding the interplay of various extrinsic and intrinsic factors on its safety and efficiency, which are being reviewed from a clinical perspective. Among extrinsic factors tourniquet cuff pressure, size and shape have been identified as key for safety and efficiency. Among intrinsic factors, limb anthropometrics, patient history and presence of cardiac, vascular, metabolic or peripheral neurologic conditions have been recognized as most important. Though there are a few potential safety concerns connected to BFRR training, the following have been identified as the most probable and health-hazardous: (a) mechanical injury to the skin, muscle, and peripheral nerves, (b) venous thrombosis due to vascular damage and disturbed hemodynamics and (c) augmented arterial blood pressure responses due to combined high body exertion and increased peripheral vascular resistance. Based on reviewed literature and authors' personal experience with the use of BFRR training in injured athletes, some guidelines for its safe application are outlined. Also, a comprehensive risk assessment *tool for screening of subjects prior to their inclusion in a BFRR training program is being introduced.*

Keywords: *blood flow restricted exercise, health risk assessment, tourniquet cuff efficiency, rehabilitation of athletes.*

VARNA UPORABA VADBE Z ZMANJŠANIM PRETOKOM KRVI

IZVLEČEK

Vadba proti majhnem uporu s sočasno zmanjšanim pretokom krvi v aktivnih mišicah (ishemična vadba) dokazano spodbuja hipertrofijo in izboljša mišično jakost primerljivo s standardno vadbo proti velikem uporu, vendar ob znatno manjši mehanski obremenitvi sklepa. Zato se ishemično vadbo pospešeno vključuje v fizioterapevtske programe, zlasti pri športnikih s poškodbami ali operativnimi posegi na sklepih spodnjih ali zgornjih udov. Kljub splošnem strinjanju glede pozitivnih učinkov na mišično zmogljivost ostaja vrsta nejasnosti glede medsebojnega učinkovanja vrste intrinzičnih in ekstrinzičnih dejavnikov, ki se pojavijo med ishemično vadbo in zelo verjetno vplivajo na njeno učinkovitost in varnost. Regulacija in velikost manšetnega tlaka ter oblika in velikost manšete so bili prepoznani kot ključni ekstrinzični dejavniki varnosti in učinkovitosti. Med intrinzičnimi dejavniki pa so bili v tem pogledu kot najbolj pomembni prepoznani sledeči: antropometrija uda in prisotnost preteklih ali sedanjih srčnih, žilnih, presnovnih ali perifernih živčnih okvar pacienta. Izmed vrste potencialnih zdravstvenih problemov, povezanih z ishemično vadbo, so najbolj verjetni in zdravje ogrožajoči (a) mehanske poškodbe kože, mišic in perifernih živcev, (b) globoka venska tromboza zaradi poškodb ožilja in spremenjene hemodinamike in (c) povečan odziv arterijskega krvnega tlaka zaradi povečanega občutka napora in upora perifernega ožilja zaradi nameščene manšete. Na podlagi objavljenih podatkov v literaturi in osebnih izkušenj avtorjev članka z uporabo ishemične vabe pri športnikih so podana priporočila za njeno varno uporabo. V članku je predstavljen tudi enostaven in razumljiv pripomoček za presojanje dejavnikov zdravstvenega tveganja posameznika pred vključitvijo v program ishemične vadbe.

Ključne besede: *vadba z oviranim pretokom krvi, ocena dejavnikov tveganja, učinkovitost manšetnega sistema, fizioterapija in rehabilitacija športnikov*

INTRODUCTION

Blood flow restricted resistance (BFRR) training, its most featured version also known as kaatsu training, has long been suggested as an alternative for conventional weight training due to the proven benefits for muscle strength and hypertrophy using relatively low resistance, hence reducing the mechanical stress across a joint. It has been used in the elderly to maintain muscle mass (Fry et al., 2010) and in athletes to improve performance (Takarada et al., 2002; Cook, Murphy & Labarbera, 2013) or to accelerate post-surgical rehabilitation (Ohta et al., 2003). Increases in muscle hypertrophy following low load BFRR training are well documented and are one of the primary reasons behind utilizing this form of exercise (Wernbom, Augustsson & Raastad, 2008). Interestingly, despite lower mechanical stress to the tissues, favourable adaptations in bone turnover have also been demonstrated with BFRR training (Karabulut et al., 2011).

However, the positive adaptation of muscle to BFRR training seems to extend beyond mimicking hypertrophic effects of high-resistance training. Namely, improvements in vascular function (Patterson & Ferguson, 2010; Hunt, Walton & Ferguson, 2012; Hunt, Galea, Tufft, Bunce & Ferguson, 2013; Evans, Vance & Brown 2010), enhanced oxygen delivery and muscle endurance (Takarada, Sato & Ishii, 2002; Kacin & Strazar, 2011) as well as cardiorespiratory endurance (Abe et al., 2010; Park et al., 2010) have been also reported with BFRR training. A recent case study even reports of an increased rate of healing in patient with osteochondral fracture (Loenneke, Young, Wilson & Andersen, 2013b).

An increasing number of published research supports the efficacy of the technique, whereas its safety has not been extensively studied. Similar to the use of surgical tourniquets on limbs of resting patients (Fitzgibbons, DiGiovanni, Hares & Akelman, 2012; Estebe, Davies & Richebe, 2011) the major concerns are due to (a) a mechanical injury to the skin, muscle, and peripheral nerves and (b) venous thrombosis due to vascular damage and disturbed hemodynamics, but also (c) augmented arterial blood pressure (ABP) responses due to combined high body exertion and increased peripheral vascular resistance induced by the tourniquet. In addition, ischemic-reperfusion injury with local or systemic effect may also play a role. The only epidemiological study available has shown a surprisingly low occurrence of any adverse effects of BFRR training other than skin bruising, in various populations in Japan (Nakajima et al., 2006). General and specific health concerns with BFRR training in healthy people have been reviewed in depth by Manini and Clark (2009), Loenneke, Wilson, Wilson, Pujol & Bemben (2011) and Pope, Willardson & Schoenfeld (2013). The present review thus addresses safety and efficiency of BFRR training from clinical perspective, in regard to a complex interplay of various extrinsic (tourniquet system and exercise) and intrinsic (anthropometrics, medical history and life style) factors. Based on reviewed evidence and our clinical experience with BFRR training in injured and operated athletes we set about developing a risk assessment tool. The tool will allow physiotherapists and non-medical staff such as strength and conditioning coaches, to manage the risk to the athletes whilst allowing them to benefit from an effective technique.

METHODS

Methods of literature review and clinical commentary were combined when preparing this manuscript. The search of scientific literature published in English language was performed until March 2015 in various electronic databases (PubMed, WoS, MEDLINE, PEDro and ScienceDirect) by the following key words and phrases: blood flow restricted exercise, ischemic training, reperfusion injury, safety and efficiency of pneumatic tourniquets and health risk assessment for vascular occlusion. Initial search gave 1582 results which were refined by use of various key word combinations and addition of new phrases most frequently associated with the topics of interest (rhabdomyolysis, reperfusion injury, contour and cylindrical cuffs, nerve injury etc.). The second selection produced 133 publications, which were further reduced to 83 entries, based on abstract content match with the topics, type of publication, research type and design, sample size and full text availability. Case studies or reports and book chapters were included only for the topics not studied by RCTs or other controlled cohort studies.

PROPOSED MECHANISMS OF MUSCLE ADAPTATION TO BFRR TRAINING

How the positive training adaptations reviewed and discussed above are elicited by muscle blood flow occlusion during exercise remains debatable. The proposed mechanisms were reviewed on several occasions, most recently and in-depth by Pope et al. (2013) and Heitkamp (Heitkamp, 2015), who listed all hypothetical physiological triggers identified so far: (a) hypoxia-induced additional or preferential recruitment of fast-twitch muscle fibers, (b) greater duration of metabolic acidosis via the trapping and accumulation of intramuscular protons (H+ ions) and stimulation of metaboreceptors, possibly eliciting an exaggerated acute systemic hormonal response, (c) external pressure-induced differences in contractile mechanics and sarcolemmal deformation, resulting in enhanced growth factor expression and intracellular signalling, (d) metabolic adaptations to the fast glycolytic system that stem from compromised oxygen delivery, (e) production of reactive oxygen species (ROS) that promotes tissue growth, (f) gradient-induced reactive hyperemia after removal of the external pressure, which induces intracellular swelling and stretches cytoskeletal structures that may promote tissue growth, and (g) activation of myogenic stem cells with subsequent myonuclear fusion with mature muscle fibers. Given that detailed review of all these mechanisms is not the primary aim of the present review, only mechanisms most closely related to the safety of tourniquet application will be discussed in the following.

When performing BFRR exercise with a pneumatic tourniquet system, a tourniquet cuff is applied to the proximal part of the upper or lower limb and inflated to the set pressure. With gradual mechanical compression of all soft tissues under the cuff, a reduction in vascular diameter is achieved, resulting in occluded venous and reduced or completely occluded arterial blood flow to the muscles at and distal to the cuff. During muscle contraction, an increase in intra-muscular pressure is generated under the pressurized cuff, further disturbing muscle blood flow. In case of isometric muscle contraction, the contraction-induced muscular pressure is basically constant, whereas during concentric/eccentric contractions it changes in a cyclical manner. If a rigid cuff with no regulation of pressure is used, effective tourniquet pressure during contractions is ~50 % higher than the set value, with ~65−75 % variation between concentric and eccentric phase of contraction (Figure 1). Depending on the cumulative degree of blood flow reduction and exercise intensity, variable levels of muscle edema, ischemia and hypoxia develop in the muscle during the exercise. Following deflation of the tourniquet, reperfusion of the limb takes place.

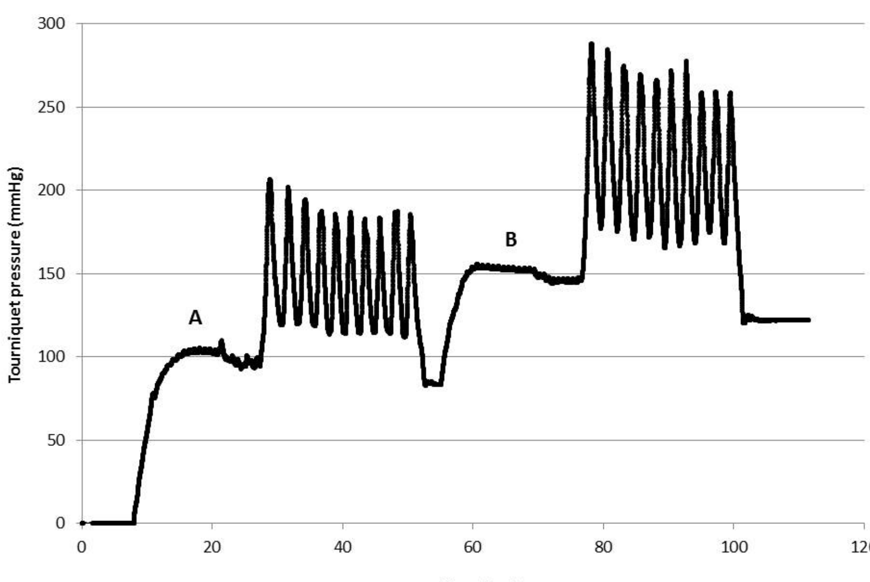

Figure 1: Cyclic changes in rigid contour tourniquet cuff (13 cm wide) pressure during ten concentric / eccentric knee-extension contractions performed at 20 % 1RM by a representative subject. Set pressures were (A) 100 mmHg and (B) 150 mmHg, with no pressure regulation provided during exercise (author's unpublished data).

There is a lack of a most optimal degree of venous and arterial blood flow reduction for muscle conditioning is. Although sound experimental evidence is still scarce, it can be assumed that two distinct changes in muscle hemodynamics are achieved during the dynamic leg exercise, by inducing either predominant venous-lymphatic occlusion (tourniquet pressure of ~60 mmHg) or intermittent complete arterial occlusion (≥150 mmHg). In the case of predominantly venous occlusion (VO), blood inflow to the muscle is not compromised, resulting in progressive rise in venous pressure (Iida et al., 2007). Given that capillary pressure is four times more sensitive to increased venous pressure, the result is augmented capillary filtration. Fluid shift from vasculature to extracellular compartments, combined with completely blocked lymphatic outflow, results in soft-tissue edema and increased interstitial fluid pressure (Levick & Michel, 2010). Consequently, some of the fluid is forced across the sarcolemma into the intracellular compartment, along with non-selective transport of various smaller molecules. Due to progressive congestion of blood in the muscle during the exercise, substantial metabolite accumulation and tissue hypoxia are eventually developed. In contrast, the resistance on both sides of the capillaries is equally reduced during complete arterial occlusion (AO) hence no detectable muscle swelling occurs during dynamic exercise. It does however substantially increase hypoxia and metabolic stress in the muscle and hence post-ischemic hyperemia. As shown by near-infrared spectroscopy, a substantial hypoxia of vastus lateralis muscle is induced after only a few initial contractions with intermittent complete AO (tourniquet pressure ≥230 mmHg, width 13 cm) (Kacin & Strazar, 2011). Upon the release of tourniquet, augmented reperfusion (active hyperemia) is driven by accumulated metabolites in the muscle cells which increases pressure gradient across sarcolemma and further cell swelling. It is speculated that cell swelling *per se* induces muscle protein synthesis (Loenneke, Fahs, Rossow, Abe & Bemben, 2012a) as it is the case with other type of cells (Lang et al., 2000). Furthermore, signs of muscle damage and prolonged (up to 48 hrs.) sarcolemmal permeability were demonstrated after only one bout of BFRR exercise (Wernbom, Paulsen, Nilsen, Hisdal & Raastad, 2012), which suggests a thin line between hypertrophic stimulus and potential muscle injury. A reduced muscle compliance to palpation can be noted after BFRR exercise, and subjects describe muscle as “hard” or “pumped up” for a short period after BFRR (authors’ unpublished observations). It was also demonstrated that transient increase in sarcolemma permeability and cell swelling is an important trigger of hypertrophy and augmented satellite cell activation (Nielsen et al., 2012). Also, muscle hypertrophy and strength gains are shown to have a good correlation (r=0.60-0.88) with metabolic stress (Takada et al., 2012; Sugaya, Yasuda, Suga, Okita & Abe, 2011). Importantly, metabolic perturbation induced by disrupted hemodynamics increases the magnitude of muscle activation, presumably of fast-twitch fibers, during low load BFRR training compared to free blood flow training of same intensity (Yasuda et al., 2009; Yasuda et al., 2014; Yasuda, Loenneke, Ogasawara & Abe, 2013). This is seen as one of the key acute adaptations which lead to strength gains following low load BFRR training (Takarada et al., 2000).

However, based on our clinical observations with preoperative conditioning of 23 athletes scheduled for ACL reconstruction, the same degree of blood flow restriction does not have the same effect on muscle activation and performance of power or endurance trained individuals of different build, even when tourniquet pressure is corrected for resting arterial pressures and leg circumference by Graham's formula (Graham, Breault, McEwen & McGraw, 1993). The number of repetitions performed was up to 40 % higher in endurance compared to power athletes (authors' unpublished observations). This may be due to different proportions of type I and type II muscle fibers and, hence, different effect of blood deprival on muscle fatigability. A similar observation was recently reported by Downs et al. (2014), who noted a ~10-15% lower rate of fatigue, calculated from the decrease in number of repetitions, for ankle plantar flexors compared to knee extensors at the same vascular occlusion, which was attributed to profoundly different muscle composition between muscle groups (Gregory, Vandenborne & Dudley, 2001). To provide sufficient training stimulus of BFRR exercise regardless of training status and muscle composition, our patients / athletes perform each exercise set to volitional failure. This, however, substantially increases the whole body exertion and cardiac load, thus patients with a history of cardiorespiratory disease must be excluded. Optimization of exercise parameters for BFRR training in different patient populations needs to be systematically addressed in further investigations.

POTENTIAL SAFETY AND EFFICIENCY ISSUES WITH BFRR TRAINING

Long-lasting (>30 min) AO induced by pneumatic tourniquets is routinely used during limb surgery in order to prevent bleeding. Tourniquet pressure above 170 mm Hg for upper and 270 mm Hg for lower limbs is usually used, which in combination with prolonged constant compression poses a threat of mechanical and, upon the release of tourniquet, ischemia-reperfusion injury of the vascular, neural, metabolic and musculoskeletal systems (Fitzgibbons et al., 2012). Ischemia is the reduction of blood supply to a tissue which results in a lack of oxygen and substrates for cellular metabolism (Ames & Nesbett, 1983). A prolonged complete ischemia and a rapid reperfusion of tissues upon the release of blood flow are the causes of reperfusion injury (Estebe, Davies & Richebe, 2011; Wakai et al., 2001; Hughes, Hendricks, Edwards & Middleton, 2010; Hughes et al., 2007). It is well known that irreversible skeletal muscle damage occurs after three hours of ischemia in normothermic conditions (Blaisdell, 2002; Pedowitz et al., 1991) but adverse cellular events begin much earlier. Research shows that reperfusion injury causes cell apoptosis, presumably by negative influences on microcirculation, subsequent local inflammatory response and production of reactive oxygen species (Blaisdell, 2002; Carden & Granger, 2000). In contrast, short episodes of ischemia – reperfusion are speculated to be the trigger for cellular adaptation to BFRR training (Wernbom et al., 2008; Manini & Clark, 2009) and were demonstrated to have both a cardio-protective (Zhu et al., 2013) and a muscle performance enhancing effect (de Groot, Thijssen, Sanchez, Ellenkamp & Hopman, 2010). However, an optimal protocol for effective and safe BFRR training remains elusive. Strength gains and hypertrophy comparable to standard high load strength training were reported with various combinations of exercise and tourniquet parameters (see (Wernbom et al., 2008; Loenneke, Wilson, Marin, Zourdos & Bemben 2012c) for review). In addition, enhanced muscle endurance capacity and hemodynamics were demonstrated with a combination of either extremely low load (40 − 50 RM) exercise and high tourniquet pressures (150 − 230 mmHg, width 13-15 cm) with reperfusion between four sets for lower limbs (Kacin & Strazar, 2011; Evans et al., 2010) or low to medium load (25 % and 50 % 1RM) exercise with low pressure (110 mmHg) without reperfusion between three sets for lower and upper limbs (Patterson & Ferguson, 2010; Hunt et al., 2012; Hunt et al., 2013). Morphologic adaptation occurred at all levels of the vascular tree with enhanced peak reactive hyperemia and transient improvement in artery function preceding changes in artery structural capacity (Hunt et al., 2013). Although tourniquet pressure is usually regarded as a key extrinsic factor of blood flow reduction, other extrinsic and intrinsic confounding factors like 1) tourniquet width and shape (Moore, Garfin & Hargens, 1987; Crenshaw, Hargens, Gershuni & Rydevik, 1988; Pedowitz et al., 1993), 2) limb circumference (Graham et al., 1993; Tuncali et al., 2006) and 3) individual's arterial blood pressures (ABP) (Newman & Muirhead, 1986; Graham et al., 1993) substantially affect the final degree of occlusion.

Influence of Tourniquet Cuff Design and Pressure

Various combinations of tourniquet pressure (range 50 − 230 mmHg) and cuff width (range 3.3 − 20.5 cm) were used in BFRR exercise studies. Although tourniquet pressures and exposure times used are lower compared to the ones in surgery, the stretching and shear forces in the tissue are most likely to be much higher due to muscle contractions under pressurized tourniquet cuff. As shown in Figure 1, the cuff pressure during concentric phase of contraction peaks ≥ 50 % above the value set on the resting muscle prior to the exercise, which reflects a very high increase in intramuscular forces at the site of cuff compression. Tourniquet system that provides a fast responsive and accurate cuff pressure regulation during muscle contractions is thus essential for a safe and efficient application of BFRR exercise.

In a resting limb, the same reduction of blood flow can be achieved using a wider tourniquet cuff at much lower pressures (Moore et al., 1987; Crenshaw et al., 1988; Pedowitz et al., 1993). Likewise, contoured (cone) cuffs induce arterial occlusion at lower pressures than straight (cylindrical) ones (Younger, McEwen & Inkpen, 2004; Pedowitz et al., 1993). Given that the shape and width of the cuff influence pressure distribution and sheer forces in the underlying muscle tissue (Pedowitz et al., 1991), using the lowest pressures possible to achieve the desired training effect should minimize the risk of soft tissue damage. Cuff width, shape and pressure also have an important influence on pain provocation and, hence, patient comfort during the application. When compared at the same inflation pressure (SBP×1.3≈160 mm Hg), wide rigid cuffs (13.5

cm) provoke somewhat higher pain levels (~2 points on Borg's CR-10) and perception of effort (~1.5 point on 6 − 20 Borg's scale) during lower limb exercise than narrow belt-like elastic cuffs (5 cm) (Rossow et al., 2012). Given that at the same pressure a wider cuff induces more blood-flow restriction, such comparisons may be deceptive. As demonstrated already by Estebe, Le Naoures, Chemaly and Ecoffey (2000) on resting upper limbs, wider cuffs (14 cm) indeed provoke more pain than narrow cuffs (7 cm) when compared at same absolute pressure (~260 mm Hg), but less pain when compared at individual occlusion pressure. The latter was on average 55 mmHg lower with wider cuffs (202 mmHg for narrow and 147 mmHg for wide cuffs) (Estebe et al., 2000), suggesting that wider cuffs might in fact provoke less discomfort and pain for the same occlusion stimulus also during the exercise. Given that different pressures and conditions (exercise vs. rest) were scrutinized in these studies, more research is needed in this regard.

In many published BFRR exercise studies, there is a lack of detailed technical characteristics of the tourniquets and pressure systems used. The degree of blood flow reduction is, thus, difficult to estimate, but according to significant differences in various confounding factors listed above, vast variations between and within studies are likely. Meta-analysis of well-designed and controlled BFRR studies (Loenneke et al., 2012c) revealed a difficulty in estimating the actual impact of various tourniquet pressures on gains in muscle mass and strength, which is not surprising due to large variations in tourniquet systems used. There is a clear need for a systematic study of differences in intramuscular responses induced by various tourniquet systems used for BFRR training.

Impact of Limb Anthropometrics on Pressure Transmission

Transmission of pressure from a tourniquet to the underlying tissues showed to be exponentially inverse to extremity circumference (Tuncali et al., 2006) and to the ratio between circumference and tourniquet cuff width (Graham et al., 1993). Similarly, significant negative correlations between tissue oxygenation and leg lean body mass, total lean body mass, and thigh circumference were reported by Karabulut, McCarron, Abe, Sato & Bemben (2011b). Furthermore, it was established that as much as ~80% of variability in the occlusion pressures with the use of rigid wide cuffs can be explained by the ratio of muscle to subcutaneous fat cross-sectional areas and only ~20% by either systolic (SAP) or diastolic (DAP) blood pressure (Loenneke et al., 2012d), which counters the previous reports (Newman & Muirhead, 1986; Graham et al., 1993). With an application of elastic belt-like tourniquet cuffs, the total variance in occlusion pressures explained by anthropometrics was much smaller, and was even non-significant for SAP. Taken together, the transmission of cuff pressure to the center of the limb, where the majority of large blood vessels is located, seems to be negatively related to the limb circumference and positively related to the cuff width.

CONSIDERATIONS FOR CLINICAL SCREENING AND RISK ASSESSMENT

The use of BFRR training for musculoskeletal rehabilitation is relatively new and rapidly evolving. To improve our understanding of the risks associated with this form of training, a thorough screening and regular auditing processes need to be established by all users of the technique.

We consider that a high quality screening process, including a medical practitioner is essential to safe guard against potential adverse reactions associated with this form of exercise. The purpose of a screen is to filter out those patients that may be at increased risk of injury for medical or other reasons. A further purpose is to identify the factors which will reduce the risk of injury to potentially overstressed structures reviewed below. Considering the safety aspects of BFRR training using these principles relies on a comprehensive personal medical, social and family history. Particular attention needs to be paid to any condition or lifestyle activity that may have impact on any of the systems outlined below. In the development of a risk assessment tool we addressed the following principles:

- identification of the structures affected by blood flow restriction;
- identification of which subjects / patients may be at higher risk from the potential negative effects of BFRR training and determination of the level of precaution required;
- development of an easy-to-use risk assessment tool;
- review of any adverse reactions;
- review and update of the risk assessment tools as necessary.

In the process of identifying potential risks, the structures which may be affected by the application of a tourniquet must be considered. We addressed each of these structures individually when determining which medical conditions may increase the risk of exposure to BFRR exercise.

Skin and subcutaneous tissues

Pressure necrosis and frictional burns can occur due to inadequate padding, poor application of the tourniquet, and movement of the fully inflated tourniquet over bare skin. Soft wrinkle-free padding should be used below the cuff (Van der Spuy, 2012) to avoid these issues. Stretch sleeves made of two-layer elastic material were shown to provide the most effective protection against skin injury during application of surgical tourniquets (Olivecrona, Tidermark, Hamberg, Ponzer & Cederfjäll, 2006). Frictional burns and pinching are more likely to occur during BFRR exercise if no padding is used.

Musculoskeletal system

In the musculoskeletal system, consideration must be given to the effect of BFRR on muscle and joints. Excessive and unaccustomed exercise may result in muscle damage and delayed-onset soreness. Both of these have also been reported after a low load BFRR training (Umbel et al., 2009), but this may be evidence of the adaptations necessary for a training effect rather than an adverse response. It was shown that excessive pressures combined with a wide tourniquet can provoke paraesthesia in the thighs during the exercise. In addition, suppressed muscle hypertrophy in vastus intermedius muscle with signs of atrophy at the site of tourniquet compression were observed after four weeks of BFRR training (Kacin & Strazar, 2011).

Lack of blood perfusion to a limb and extreme physical exertion are both well-known causes of rhabdomyolysis. This is a clinical syndrome resulting from skeletal muscle damage and the release of potentially toxic substances into the circulation (Allison & Bedsole, 2003). It may be caused by trauma or muscle hypoxia and manifests as muscle pain and weakness. There was also a case report of rhabdomyolysis following the initial exposure to BFRR training (Iversen & Rostad, 2010). Other potential causes of rhabdomyolysis, which need to be excluded prior to BFRR training, are outlined in Table 1.

Consideration must, therefore, be given in the case when other conditions associated with rhabdomyolysis are present. This includes restricted calorific intake (particularly with low levels of potassium, phosphate and magnesium), a history of severe heat illness / injury, a recent muscle trauma or a crush injury. Caution must, therefore, be taken in individuals who lack any previous training history as unaccustomed exercise can also be associated with an increased risk of rhabdomyolysis.

The personal experience of the authors is of the use of BFRR in the rehabilitation of musculoskeletal injuries. When determining potential risk factors for the use of this technique in patients after ACL reconstruction with or without partial menisectomy (N=32), we were concerned about the potential negative effect on post-surgical patients with a swollen joint, due to congestion of tissues or swelling that may result from the external restriction of blood and lymphatic vessels. This may also have impact on those with an inflammatory arthropathy, synovitis, haemarthrosis or septic arthritis. Indeed, in case of post-surgical synovitis (N=1) or haemarthrosis (N=1) exacerbation of symptoms were induced by BFRR (authors' unpublished observations), hence, alternative forms of training should be considered.

Table 1: Types and causes of rhabdomyolysis. (Allison & Bedsole, 2003)

Type	Cause
Trauma or muscle compression	*Crush syndrome*
	Prolonged immobilization
Non-traumatic exertional rhabdomyolysis	*Unaccustomed exertion* in untrained individuals
	Hyperthermia: malignant hyperthermia, neuroleptic malignant syndrome
	Metabolic myopathies: mitochondrial myopathies, McArdles etc
Non-traumatic and non-exertional rhabdomyolysis	*Drugs*: alcohol, heroin, cocaine, amphetamines, methadone, and D-lysergic acid diethylamide (LSD), antipsychotics, statins, selective serotonin reuptake inhibitors, zidovudine, colchicine, lithium, antihistamines, and several others
	Toxins: metabolic poisons, such as carbon monoxide, snake venoms, insect venoms, including wasp and bee stings, mushroom poisoning
	Viral infections: acute viral infections (eg influenza A and B), coxsackievirus, Epstein-Barr, herpes simplex, parainfluenza, adenovirus, echovirus, human immunodeficiency virus, and cytomegalovirus
	Bacterial infections: bacterial pyomyositis legionella, tularemia, streptococcus and salmonella, E. coli, leptospirosis, coxiella burnetii (Q fever), and staphylococcal infection
	Electrolyte disorders: hypokalemia, hypophosphatemia, diabetic ketoacidosis or nonketotic hyperglycemia, hypophosphatemia, hypocalcemia hyponatremia hypernatremia
	Inflammatory myopathies: inflammatory myopathies, dermatomyositis, polymyositis
	Endocrine disorders: diabetes, hyper and hypo-thyroidism

Cardiac function and arterial blood pressure

In healthy population, a substantially higher exercise-induced increase in SAP, DAP and mean ABP and heart rate (HR) compared to free flow exercise were found after two or more subsequent sets of BFRR exercise with no reperfusion between the sets (Renzi, Tanaka & Sugawara 2010; Vieira, Chiappa, Umpierre, Stein & Ribeiro 2013; Takano et al., 2005). As demonstrated by Renzi et al. (2010), increased HR during blood flow restricted walking exercise (cuff pressure 160 mmHg, width not reported) compensates for a compromised venous return and, hence, reduced the stroke volume, which results in a three-fold greater index of myocardial oxygen demand. A report by Vieira et al. (2013) corroborates the exaggerated heart rate (HR) and ABP responses to single-arm BFRR exercise (cuff pressure 120 mmHg, width not reported) performed at 30 % 1RM in both young and older healthy men. Similar findings were recently reported for unilateral leg BFRR exercise with two different tourniquet cuff pressures (1.3×DAP and 1.3×SAP, width 6 cm), with the exception of an attenuated rather than augmented HR response (Downs et al., 2014). It appears that BFRR exercise can either increase or decrease a normal HR response, depending on the interplay between cardio acceleration driven by increased sympathetic drive and reduced stroke volume and cardio deceleration driven by increased cardiac afterload and decreased preload. These findings show that a lack of reperfusion during the short rest between exercise sets progressively exacerbates cardiac load and cardiovascular demand. However, if exercise protocols are not matched for work and intensity, but performed until volitional failure, acute HR and ABP responses are similar between BFRR and free flow exercise (Loenneke et al., 2012b; Kacin, Strazar, Palma & Podobnik 2011; Kacin & Strazar, 2011). From clinical perspective it is important that cardiac and blood pressure responses to low-load BFRR exercise are still significantly lower than during the standard high-load resistance exercise despite a higher perception of exertion (Poton & Doederlein Polito, 2014). The latter is apparently driven predominantly by peripheral sensations from the occluded limb. Given that a low load BFRR exercise does not induce post-exercise hypotension comparable to a free flow high load resistance exercise (Rossow et al., 2011), it appears that an overall level of exertion determines systemic cardiovascular responses, more than blood flow restriction *per se*.

The safety of BFRR exercise in patient populations at increased risks for cardiovascular events has not been systematically studied so far. A recent pilot study of nine patients with stabile ischemic cardiac disease (Madarame, Kurano, Fukumura, Fukuda & Nakajima, 2013) also revealed an augmented exercise-induced increase in heart rate and plasma noradrenaline concentration during the BFRR exercise, although the subjects performed a fixed number of repetitions per set rather than exercising to volitional failure. Despite an increased body exertion, no warning signs of any cardiovascular events were observed in these patients (Madarame et al., 2013). Thus, subjects with a history of or an increased risk of cardiovascular disease should be thoroughly screened prior to their inclusion to BFRR training program and closely monitored for excessive HR and ABP responses during the exercise. Exercise is advised not to be performed to volitional failure and should also allow longer and more frequent reperfusion during multiple sets. In our experience, six sets of BFRR with 45 − 60s reperfusion between two consecutive sets is better tolerated by ACL deficient (N=32) patients or those with knee osteoarthritis (N=12), than three or four sets without reperfusion. It can be assumed that such BFRR exercise protocol is also more appropriate for people with moderate risk for cardiovascular events. An alternating exercise for agonistic and antagonistic muscles can further reduce the stress, but most likely reduces the BFRR exercise effect.

Little is known about the long-term effects of BFRR training on cardiovascular regulation. A study of Kacin and Strazar (2011) revealed a small, but significant increase in pre-exercise resting diastolic arterial pressure after a 4-week BFRR training program, which may indicate chronically elevated levels of stress hormones due to repetitive high body exertion in healthy individuals. This observation warrants a further investigation both in healthy individuals and cardiac patients.

Vascular considerations

Overall, there is evidence that there are vascular benefits to the use of blood flow restriction (Patterson & Ferguson, 2010; Hunt et al., 2012; Hunt et al., 2013), however, blood flow through vessels is affected by a number of factors including the vessel diameter and blood turgidity. Any condition that interferes with a 'normal' blood flow may contribute to and compound these compressive effects by impacting on the turgidity of the blood. It stands to reason that any condition affecting blood flow through the limb to be trained and the wider cardiovascular system may show impact on the risk to the patient. Nakajima estimated the risk of venous thrombus to be 0.055 % in their epidemiological study in Japan (Nakajima et al., 2006), nonetheless it is very low, it is a real risk. Consideration must therefore be given to a personal or family history of conditions affecting blood flow through local vessels or the wider cardiovascular system. These are outlined in Table 2.

Table 2: Medical and social factors which may affect limb muscle blood flow.

Lifestyle	*Travel* *Periods of immobilization* *Medication* *Smoking*
Personal Medical History	*Clotting disorders* *Connective tissue disorders* *Thrombosis (deep vein, pulmonary embolus, stroke)* *Traumatic injury to blood vessels or nerves, compartment syndrome, fractures or surgery* *Non traumatic injury etc. diabetes/ hypertension/ peripheral vascular disease* *Liver/ renal disease* *Pregnancy*
Family History	*Clotting disorders* *Connective tissue disorders* *Sickle cell anemia*

Despite the potential risk, there is a growing body of evidence that BFRR exercise does not increase risk of venous thrombosis, at least in healthy individuals. A single bout of blood flow restriction exercise show to augment fibrinolytic potential (Clark et al., 2011) without affecting coagulation (Clark et al., 2011; Madarame et al., 2010; Fry et al., 2010) and inflammatory responses (Clark et al., 2011). The question whether this holds true also for patients with increased risk for cardiovascular events has not been systematically studied yet. A recent pilot study of Madarame et al. (2013) showed that hemostatic and inflammatory responses are not significantly increased by a single bout (4 sets without reperfusion) of BFRR exercise performed at 20 % 1RM (5 cm wide elastic cuff with pressure 200 mmHg) in patients with stabile ischemic heart disease. However, these results should not be directly extrapolated to other patient populations and the interpretation must be taken with caution; the number of subjects was rather small and the degree of blood flow restriction must have been different between subject at a given tourniquet pressure.

Neural Considerations

Disruptions in peripheral nerve function may be due to both compression and local asphyxiation (Ochoa, Fowler & Gilliatt, 1972). Under lower levels of compression, disruptions are usually due to local ischemia (Brown & Brenner, 1944) unless the duration of compression is prolonged, in which case disruption is due to the pressure effects alone. In experiments looking into the effects of tourniquet pressure on the tissues beneath it, higher pressures have been shown to cause localized conduction block as a result of mechanical deformation nerve fibers (Ochoa, Fowler & Gilliatt, 1972), with large nerve fibers being affected more than those that are smaller (Bolton & McFarlane, 1978; Larsen & Hommelgaard, 1987). Lundborg, Gelberman, Minteer-Convery, Lee & Hargens (1982) reported hand numbness resulting from tourniquet compression of arm likely due to nerve ischemia and conduction block, with similar numbness reported also in the thigh during the BFRR exercise by Kacin and Strazar (2011). Such acute nerve compression, however, does not usually have a long-term negative effect on nerve conduction velocities, at least in healthy adults (Clark et al., 2011).

It is well known that peripheral nerve function (both sensory and motor) in diabetics is reduced early in the disease and that this is also likely to be due to ischemia (Gregersen, Servo, Borsting & Theil, 1978) although the deterioration in nerve function can be reduced by maintaining good control of blood sugars. Therefore, the relative risk of nerve injury in diabetics using BFRR may be considered to be higher than in the general population. In assessing risk, it also stands to reason that any history of previous disruption to the peripheral nervous system particularly if due to compression, places a patient at a higher risk of re-injury during BFRR training. Caution is particularly advised in paralympic athletes with a spinal cord injury, direct peripheral nerve injury (such as post-traumatic joint dislocation) or a complex regional pain syndrome.

Metabolic and systemic conditions

There is good evidence that BFRR training is beneficial in diabetics (Satoh, 2011). However, besides the potential risk of adverse neural effects described above, there is a well-documented increased risk of peripheral vascular disease with disordered regulation of cutaneous blood flow and increased susceptibility to leg ulcers and limb loss in this population (Sima, Thomas, Ishii & Vinik, 1997). There is an argument that any method that restricts blood flow may compound these issues. In athletes with diabetes, there is a likelihood of fewer other confounding risk factors than in non-athletic diabetic patients. We would, nevertheless, consider that, before using this form of training in a diabetic athlete, a medical assessment of the overall risk versus benefit for the individual should be undertaken. In addition, based on the extensive Kaatsu work in Japan (Nakajima et al., 2006) the risks of adverse effects are not as high as may be first considered, so this valuable method of training should not be automatically excluded. In other diabetic populations the risk may be higher and each person should be assessed individually as to their suitability.

Paralympic athletes may include those with Duchene muscular dystrophy. This is a condition in which the protein, dystrophin, is absent and causes an increase in sarcolemma damage in response to the exercise (Markert, Ambrosio, Call & Grange, 2011). Loenneke et al. (2013a) suggested that BFRR may be a good way to improve symptoms in this group of patients for whom exercise may improve their condition, but may also be associated with muscle damage, as discussed above. In considering the use of BFRR training in paralympic athletes and other people with this condition, sound medical reasoning was used in the authors' clinical practice whilst acknowledging the absence of strong medical evidence as to its risks or benefits.

Other less common conditions for consideration and rarely seen in our population, include genetic muscle diseases comprising familial paroxysmal rhabdomyolysis, McArdles, myopathies, and severe hypothyroidism. The only published evidence on these conditions is a case study in Inclusion Body Myositis in which a patient gained improvements in strength and motor function after BFRR training with no adverse effects on his disease (Gualano et al., 2010). Certain medication such as statins and some medications for Parkinson's disease are also associated with this, which also increases the risk of adverse effects (Table 1).

DEVELOPING A RISK ASSESSMENT TOOL

Considering the safety aspects of BFRR training using these principles relies on a comprehensive personal, medical, social and family history. Particular attention needs to be paid to any condition or lifestyle activity that may impact on any of the systems outlined above. In recognition of this the following screening tool was developed (Figure 2).

MAGNITUDE OF RISK	MEDICAL HISTORY OR LIFESTYLE FACTOR	PATIENT RESPONSE	DECISION
ABSOLUTE	Do you have a family history of clotting disorders (e.g. SLE (lupus), haemophilia, high platelets)?	YES	STOP
		NO	CONTINUE
	Do you have level 1 hypertension (SAP ≥ 140 mmHg)?	YES	STOP
		NO	CONTINUE
	Do you have a past history of DVT or pulmonary embolus?	YES	STOP
		NO	CONTINUE
	Have you suffered from a haemorrhagic or thrombotic stroke?	YES	STOP
		NO	CONTINUE
RELATIVE	Do you have a family history of clotting disorders (e.g. SLE (lupus), haemophilia, high platelets)?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you smoke?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Are you on any medication including the contraceptive pill?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have a history of injury to your arteries or veins?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have a history to any of your nerves (including back or neck injury)?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have diabetes?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Does one of your parents or siblings have diabetes?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have hypertension (SAP 120-140 mmHg)?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have metal work in situ?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have any undiagnosed groin/calf pain?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have/have you suffered from compartment syndrome?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Have you had surgery in past 4 weeks?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Have you had a journey lasting more than 4 hours or a flight in the last 7 days?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE
	Do you have any other medical conditions including a history of synovitis?	YES	SEEK MEDICAL ADVICE
		NO	CONTINUE

Figure 2: Clinical screening tool for risk assessment of subjects prior to their inclusion in blood flow restricted resistance training program.

If it is considered that an athlete may benefit from BFRR training, they ought to be subjected to a series of questions to determine whether their medical history or lifestyle may increase the risk of illness or injury when using BFRR training. The purpose of the questions is to assess whether the athlete is at higher than normal risk of adverse reactions or injury whilst using this form of training. The risk factors were separated into 'absolute' and 'relative', where the following absolute risk factors were recognized:

- history or presence of clothing disorders (including SLE, hemophilia and high plateles count);
- history or presence of deep vein thrombosis (DVT) or pulmonary embolism;
- history of thrombotic or haemorrhagic stroke;
- presence of level 1 hypertension or higher.

If patients / athletes show an absolute risk factor then they are automatically excluded from BFRR training. If they do not, then they are able to continue with the assessment tool. If they showany relative risk factor, a referral is made to a medical practitioner prior to progression with BFRR training. The tool was designed so it can be used at the point of contact by a non-medical practitioner, but with a clear understanding that the final decision about the suitability of an athlete for BFRR is ultimately a medical one.

The following precaution measures in different patient populations are suggested:

1. Where there may be an increased risk of thrombotic events screening should be considered and at the very least, close monitoring is advised and a low threshold maintained for using a different form of resistance training.
2. Subjects with a history or increased risk of cardiovascular disease should be thoroughly screened prior to their inclusion to BFRR training program and closely monitored for excessive HR and ABP responses during the exercise. The exercise not performed to volitional failure with longer and more frequent reperfusions allowed during multiple sets is also advised.
3. Those who may be at a higher risk of nerve injury such as diabetics should be fully examined for evidence of current compromise and monitored for any changes in sensation, or development of paraesthesia in the exercising limb. In these subjects, monitoring blood glucose levels should be considered and in those with poorly controlled diabetes, other forms of training may be advisable.
4. In all subjects, but particularly where factors that may contribute to the development of rhabdomyolysis exist, monitoring for excessive muscle pain and weakness, changes in urine color and systemic symptoms of malaise are essential during BFRR training. Where there is a high level of suspicion, appropriate medical advice should be sought early and training should be ceased.

CONCLUSIONS

Tourniquet design and pressure and whether a patient / athlete is at a high risk of adverse reactions are the two key considerations which can be managed to increase the safety and efficiency of BFRR training. A pneumatic tourniquet is very easy to use, but is a rather crude method of blood flow restriction, hence, a safe and efficient application can be provided only by well-controlled tourniquet pressure on tissues. The degree of blood flow reduction and tissue compression induced by pneumatic cuffs during dynamic exercise most likely varies greatly between subjects in published studies, thus, precise parameters for a safe and efficient application cannot be established from available data. Tourniquet pressure during BFRR training should be set individually, where at least subject's limb circumference and composition (skinfold), arterial blood pressures and cuff design (width and shape) are to be taken into the account. We consider that a high quality screening process including a medical practitioner is the best way to safeguard against adverse reactions associated with this form of exercise. To improve our understanding of the risks associated with BFRR training, a thorough and regular auditing process needs to be established.

Conflicts of interest

Authors declare no conflict of interest or financial benefit connected with this manuscript.

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