Blood-flow-restricted exercise: strategies for enhancing muscle adaptation and performance in the endurance-trained athlete

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REVIEW ARTICLE

Blood-flow-restricted exercise: Strategies for enhancing muscle adaptation and performance in the endurance-trained athlete

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Abstract

A key objective of the training programme for an endurance athlete is to optimize the underlying physiological determinants of performance. Training-induced adaptations are governed by physiological and metabolic stressors, which initiate transcriptional and translational signalling cascades to increase the abundance and/or function of proteins to improve physiological function. One important consideration is that training adaptations are reduced as training status increases, which is reflected at the molecular level as a blunting of the acute signalling response to exercise. This review examines blood-flow-restricted (BFR) exercise as a strategy for augmenting exercise-induced stressors and subsequent molecular signalling responses to enhance the physiological characteristics of the endurance athlete. Focus is placed on the processes of capillary growth and mitochondrial biogenesis. Recent evidence supports that BFR exercise presents an intensified training stimulus beyond that of performing the same exercise alone. We suggest that this has the potential to induce enhanced physiological adaptations, including increases in capillary supply and mitochondrial function, which can contribute to an improvement in performance of endurance exercise. There is, however, a lack of consensus regarding the potency of BFR training, which is invariably attributable to the different modes, intensities and durations of exercise and BFR methods. Further studies are needed to confirm its potential in the endurance-trained athlete.

KEYWORDS
blood-flow-restricted exercise, capillary, ischaemic training, mitochondria, sport performance

1 | INTRODUCTION

A key objective of the training programme for an endurance athlete is to optimize the underlying physiological determinants of performance (Figure 1). Training-induced adaptations of these determinants are governed by the intensity, duration and overall volume of the training sessions. The mechanisms by which the stressors associated with exercise are sensed and translated into improved physiological function remain unresolved. One common theory is that these stressors initiate transcriptional programmes and post-translational

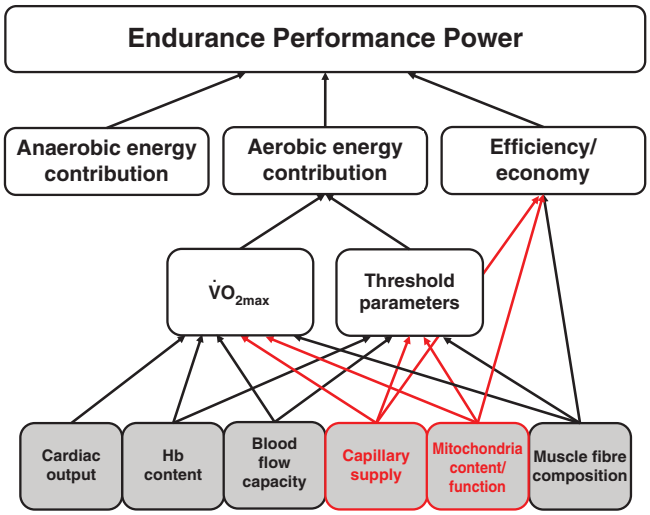

FIGURE 1 Schematic diagram of the physiological factors that interact as determinants of endurance performance velocity or power output. Figure modified from Joyner & Coyle (2008). Specific focuses of this review (capillary supply and mitochondrial content/function) are highlighted in red. There are close correlations between capillary density and cycling maximal oxygen uptake ($\dot{V}_{O_2\,max}$) (Saltin et al., 1977), time to exhaustion during high-intensity endurance exercise (Coyle et al., 1988) and critical power (Mitchell et al., 2018). Endurance training (~70–80% of $\dot{V}_{O_2\,max}$) can induce capillary growth in skeletal muscle of previously untrained individuals (Andersen & Henriksson, 1977). There is a close correlation between markers of mitochondrial density and $\dot{V}_{O_2\,max}$ (Flück, 2010; Jacobs & Lundby, 2013). Skeletal muscle maximal oxidative phosphorylation capacity is a predictor of time-trial performance in well-trained cyclists ($\dot{V}_{O_2\,max}$ ~70 ml min^{-1} kg^{-1}; Jacobs et al., 2011). Multiple training modes induce increases in a range of markers of mitochondrial content (Hoppeler et al., 1985; Perry et al., 2010). Abbreviation: Hb, haemoglobin

New Findings

- **What is the topic of this review?**
  Blood-flow-restricted (BFR) exercise represents a potential approach to augment the adaptive response to training and improve performance in endurance-trained individuals.
- **What advances does it highlight?**
  When combined with low-load resistance exercise, low- and moderate-intensity endurance exercise and sprint interval exercise, BFR can provide an augmented acute stimulus for angiogenesis and mitochondrial biogenesis. These augmented acute responses can translate into enhanced capillary supply and mitochondrial function, and subsequent endurance-type performance, although this might depend on the nature of the exercise stimulus. There is a requirement to clarify whether BFR training interventions can be used by high-performance endurance athletes within their structured training programme.

modifications essential for increasing the abundance and/or function of specific proteins that ultimately improve physiological function (Perry & Hawley, 2018). Therefore, it is important to consider the nature of each single exercise stress and the consequent adaptive mechanisms when constructing the weekly training micro-cycle and the broader, periodized macro-cycle of the individual athlete.

An important consideration is that training adaptations are reduced as training status increases (e.g., Laursen & Jenkins, 2002). This is reflected at a molecular level as a blunting of the signalling response to a single session of exercise (Flück, 2010; Granata et al., 2020; Perry et al., 2010). The question is, therefore, what interventions can be used to augment the stress and subsequent signalling response to exercise which, if repeated over time, will lead to enhanced physiological adaptation and endurance performance, particularly in trained populations? Several strategies have been considered in the pursuit of enhanced adaptation, such as manipulation of training intensity distribution (Seiler, 2010) and nutritional interventions (Rothschild & Bishop, 2020). In this review, we examine the evidence for exercise performed with blood flow restriction (BFR) as an effective strategy to augment the exercise-induced stress and subsequent signalling responses to enhance the physiological characteristics of the endurance athlete.

2 | DETERMINANTS OF ENDURANCE PERFORMANCE AND SCOPE OF REVIEW

Endurance exercise performance is defined as the ability to sustain dynamic exercise for extended periods of time (typically, >15 min), including high-intensity intermittent exercise. Endurance performance is largely determined by the maximal power of the aerobic energy system and the fraction of this power that can be sustained (Joyner & Coyle, 2008). These determinants are primarily reflected by maximal oxygen uptake ($\dot{V}_{O_2\,max}$) and threshold parameters (e.g., lactate threshold and critical power). The power and capacity of anaerobic metabolic processes also contribute, particularly when exercise is performed in the heavy- and severe-intensity domains, where there is a significant anaerobic contribution to total ATP turnover. The efficiency with which total energy turnover is converted to external work also has a major impact. These determinants of endurance performance are limited by several physiological factors (see Figure 1). The focus of the present review is on adaptations associated with capillary growth and mitochondrial biogenesis, because much of the published research on BFR training in relationship to endurance performance has been concentrated on these factors.

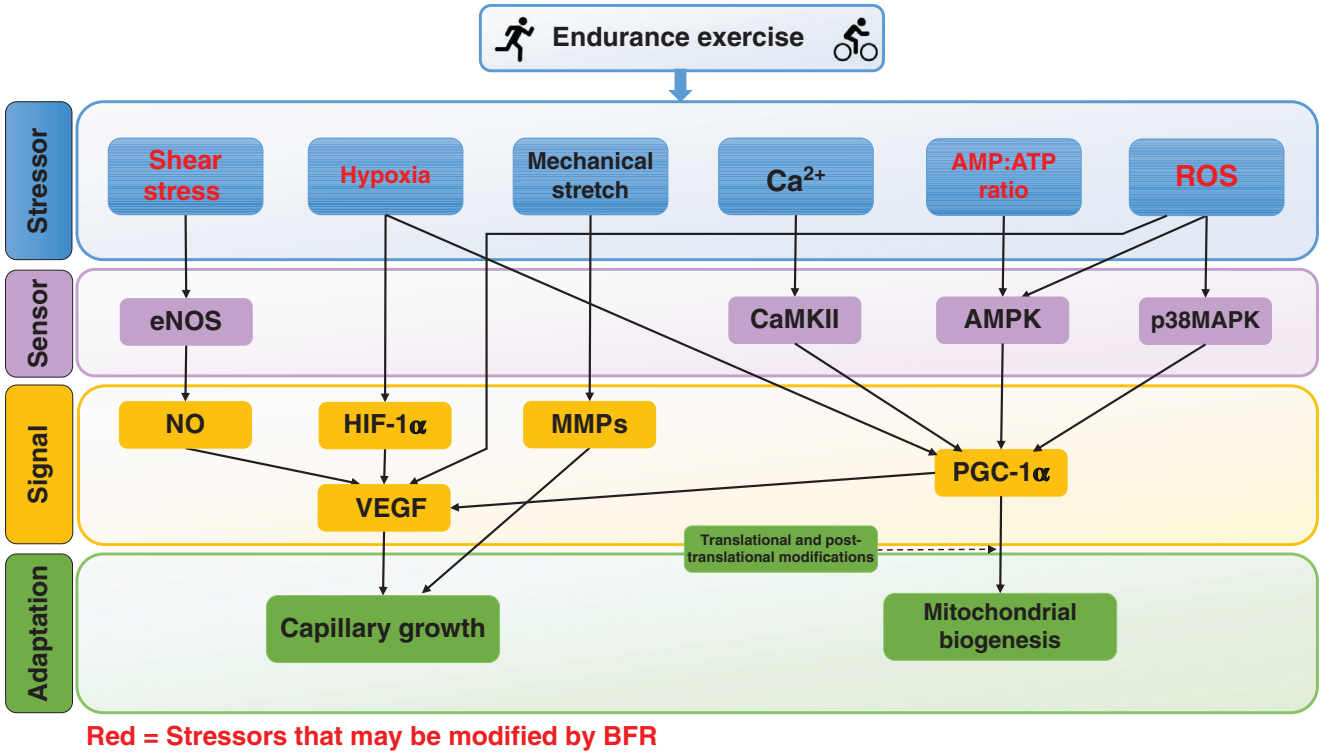

FIGURE 2 Schematic diagram of the key components of the known signalling pathways likely to elicit exercise-induced capillary growth and mitochondrial biogenesis. Candidates of physiological stressors that might be modified by blood flow restriction are indicated in red. Abbreviations: AMP, adenosine monophosphate; AMPK, 5' adenosine monophosphate-activated protein kinase; ATP, adenosine triphosphate; Ca2+, calcium ion; CaMKII, calmodulin-dependent protein kinase II; eNOS, endothelial nitric oxide synthase; HIF-1α, hypoxia-inducible factor-1α; MMPs, matrix metalloproteinases; NO, nitric oxide; PGC1-α, peroxisome proliferator-activated receptor-γ coactivator 1-α; p38MAPK, p38 mitogen-activated protein kinase; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor

3 | PHYSIOLOGICAL AND MOLECULAR SIGNALS FOR ADAPTATION

The mechanisms underlying the adaptive response to exercise training have been proposed to involve transient physiological and metabolic perturbations that activate molecular signalling pathways within skeletal muscle and endothelial cells (Figure 2).

3.1 | Capillary growth

The growth of new capillaries from an existing capillary bed, termed angiogenesis, is stimulated by several exercise-related stressors. One key signal is shear stress, which is the tangential, frictional force exerted on the luminal side of endothelial cells as blood flows along their surface, which increases as blood flow velocity increases (Hudlicka & Brown, 2009). Reduced oxygen tension (i.e., hypoxia) is also thought to play a role in capillary growth (Egginton, 2009). These stressors promote the activation of endothelial cell signalling pathways (Chien, 2007), including vascular endothelial growth factor (VEGF), a crucial pro-angiogenic factor in skeletal muscle (Olfert et al., 2010), which stimulates endothelial cell proliferation and migration, hence angiogenesis (Egginton, 2009). Many studies have demonstrated that VEGF is essential for exercise-induced angiogenesis (Delavar et al., 2014; Olfert et al., 2010). The VEGF-mediated angiogenic response to shear stress is regulated mainly by nitric oxide (NO), which is released in proportion to endothelial nitric oxide synthase (*eNOS*; *NOS3*) activity that increases with increasing shear stress (Egginton, 2009; Hudlicka & Brown, 2009). The angiogenic response to hypoxia is mediated, in part, by an increase in the activity of hypoxia-inducible factor-1 (HIF-1) and, in particular, its subunit HIF-1α (Rey & Semenza, 2010). This subunit is sensitive to oxygen levels and, upon activation in hypoxic conditions, translocates to the nucleus, where it induces the expression of multiple gene targets, including *VEGF* (Forsythe et al., 1996).

3.2 | Mitochondrial biogenesis

Mitochondrial biogenesis can be defined as the making of new components of the mitochondrial reticulum (Granata et al., 2018) and can include changes in mitochondrial content, mitochondrial respiratory function or other aspects of mitochondrial quality, such as the density of the cristae or supercomplex formation. Exercise-induced mitochondrial biogenesis is initiated by homeostatic perturbations (Coffey & Hawley, 2007), which activate protein kinases [e.g., calmodulin-dependent protein kinase II (CaMKII), p38 mitogen-activated protein kinase (p38MAPK) and 5′-adenosine monophosphate-activated protein kinase (AMPK)], which, in

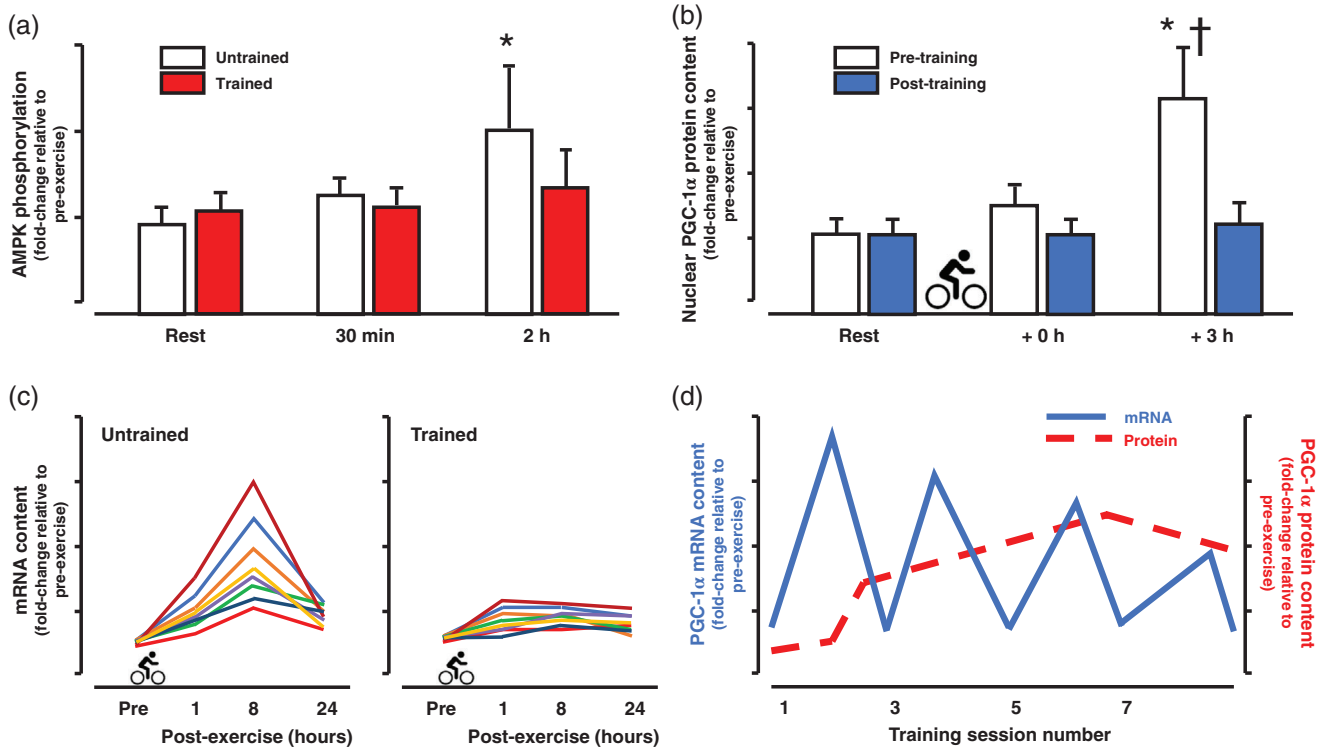

FIGURE 3 Experimental evidence demonstrating the blunting of the exercise-induced signalling response after endurance exercise training. (a) Lack of activation of skeletal muscle 5′-adenosine monophosphate-activated protein kinase (AMPK) during 120 min of cycling exercise at ~65% of maximal oxygen uptake ($\dot{V}_{O_2\,max}$) in untrained ($\dot{V}_{O_2\,max}$ ~38 ml min^{-1} kg^{-1}) compared with endurance-trained ($\dot{V}_{O_2\,max}$ ~62 ml min^{-1} kg^{-1}) individuals (figure modified from McConnell et al., 2020). (b) Blunting of protein expression of nuclear fraction of peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) after 20 days of high-volume (40 sessions), high-intensity interval training (figure modified from Granata et al., 2020). (c) Blunting of the exercise-induced mitochondrial and angiogenic transcript response after the elevation of mitochondrial volume density by endurance training. Participants exercised at the same relative intensity (65% of maximal aerobic power) in the untrained and trained state (6 weeks, five times per week for 30 min at 65% of maximal aerobic power; figure modified from Flück, 2010, based on the data of Schmutz et al., 2006). (d) Temporal responses of *PGC-1α* mRNA and PGC-1α protein throughout 2 weeks of high-intensity interval training in recreationally active participants (figure modified from Perry et al., 2010)

turn, phosphorylate transcription factors and/or transcriptional coactivators involved in the regulation of DNA transcription (Hood, 2009). These events promote a transient increase in the mRNA content of kinases, transcription factors, (co)activators and downstream proteins, increasing the potential for mRNA translation and the subsequent formation of precursor proteins in the mitochondria (Ljubicic et al., 2010). Peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC-1α) is a key transcriptional coactivator coordinating mitochondrial biogenesis (Puigserver & Spiegelman, 2003), which is also an important pro-angiogenic factor (e.g., Arany et al., 2008).

4 | THE ADAPTIVE SCOPE OF TRAINED MUSCLE

Endurance-trained individuals, defined as those with a $\dot{V}_{O_2\,max}$ of >65 ml min^{-1} kg^{-1}, are typically accustomed to varied and voluminous exercise stimuli, such that an increase in training volume alone is insufficient to improve performance (Costill et al., 1988; Hoppeler et al., 1985). The reduced adaptability of trained individuals is also reflected at the tissue level. Cross-sectional and longitudinal studies have demonstrated that the large increases in skeletal muscle capillarity and oxidative enzyme activity (citrate synthase, succinate dehydrogenase and cytochrome oxidase) during the first few months of endurance training are progressively attenuated as training is continued (e.g., Saltin et al., 1977).

This attenuated adaptive potential of skeletal muscle as it becomes more trained is also demonstrated in the acute signalling changes during exercise. Blunted exercise-induced increases in the activity, phosphorylation state or content of AMPK (Figure 3a) (McConell et al., 2005, 2020) and PGC-1α (Figure 3b) (Granata et al., 2020) have been observed after only 2–3 weeks of endurance training in recreationally active men. Other studies have shown that increases in skeletal muscle expression of mitochondrial and angiogenic mRNA transcripts after a single exercise session are blunted after short periods of endurance training in untrained individuals (Figure 3c,d) (Flück, 2010; Granata et al., 2020; Høier et al., 2012; Jensen et al., 2004; Perry et al., 2010; Richardson et al., 2000; Schmutz et al., 2006).

The reduced plasticity of trained skeletal muscle suggests that adaptations in highly trained individuals primarily serve to maintain their physical performance and/or that the training stimulus is

insufficient to promote further adaptation. These observations demonstrate the necessity for introducing variations in training to prevent the attenuation of the molecular signalling responses that drive long-term adaptations essential for the enhancement of performance. Moreover, as an athlete's training volume and intensity increase, this consideration becomes more important, particularly to avoid over-training and/or injury.

5 | CAN BLOOD-FLOW-RESTRICTED EXERCISE BE USED TO ENHANCE THE ENDURANCE EXERCISE STIMULUS?

Blood flow restriction or complete circulatory occlusion has been used for many years to permit a greater understanding of physiology (e.g., Bull et al., 1989), metabolic function (e.g., Greenhaff et al., 1993; Larsson & Bergström, 1978) and the adaptive responses to exercise interventions (e.g., Esbjörnsson et al., 1993; Sundberg et al., 1993). In an early series of investigations, blood flow was restricted to the legs by placing the participants' legs inside a hyperbaric chamber (Eiken & Bjurstedt, 1987), in which the pressure was increased to 50 mmHg above atmospheric pressure. This caused a decrease of ~20% in leg blood flow during knee-extensor exercise at the prescribed submaximal work rates (Sundberg & Kaijser, 1992). Blood flow restriction is more commonly applied using an inflatable cuff (Abe et al., 2006), a tourniquet (Shinohara et al., 1998) or an elastic bandage (Loenneke et al., 2010) around the proximal portion of the limb to restrict arterial inflow and prevent venous outflow from the exercising muscles. Recently, a gravity-induced BFR exercise model was developed, whereby cycling was performed with the participants' legs above the level of the heart, which promoted deoxygenation in the exercising muscles in comparison to cycling with the legs below the heart (Preobrazenski et al., 2020).

Multiple variables of cuff application can be manipulated, which has a significant impact on the level of BFR and associated physiological/metabolic responses. Wide cuffs are more effective than narrow cuffs in restricting arterial blood flow at lower inflation pressures (Crenshaw et al., 1988). Compared with wide cuffs (13.5 cm), complete arterial occlusion did not occur using narrow cuffs (5 cm) in some individuals, even at pressures of ≤300 mmHg (Loenneke et al., 2012). Cuff pressure also has a significant impact on the level of BFR. In many studies, it has been common to inflate the cuff to the same absolute pressure (e.g., Credeur et al., 2010; Evans et al., 2010; Kacin & Strazar, 2011; Takarada et al., 2000). However, owing to inter-individual anthropometric and physiological differences (e.g., limb circumference, subcutaneous fat and arterial blood pressure), a standard occlusion pressure might not reduce blood flow to the same degree in different individuals. Moreover, a sex difference in the cuff pressure required to achieve a given level of BFR has been reported (Hunt et al., 2016). Therefore, it has been proposed that the level of BFR should be set relative to the individual (Patterson et al., 2019).

Another important factor to consider is the timing of cuff application in relationship to exercise. In many studies, the cuff is inflated immediately before exercise and remains inflated throughout exercise and during the recovery periods between exercise bouts (Scott et al., 2015). In other studies, the cuff is released during the recovery periods (Christiansen et al., 2018, 2019a, b, 2020), which provides additional episodes with reperfusion. If the exercise intensity is high, it is more feasible to use postexercise BFR, whereby the cuff is inflated rapidly upon completion of each exercise interval and deflated before the subsequent exercise bout (Mitchell et al., 2019; Taylor et al., 2016).

Based on the evidence above, many variables inherent to the BFR exercise protocol can be adjusted, depending on the purpose of the exercise session, to achieve a desired degree of blood circulation and physiological stress in the exercising muscles.

6 | PHYSIOLOGICAL SIGNALS ALTERED BY BLOOD-FLOW-RESTRICTED EXERCISE

The changes in blood flow caused by BFR during exercise and/or in the recovery from exercise expose the peripheral vasculature and exercising skeletal muscle to a distorted level of blood perfusion and oxygenation that gives rise to shear, hypoxic, metabolic and oxidative stress signals. These stressors play putative roles in the adaptive response of the microvasculature and skeletal muscle.

6.1 | Skeletal muscle blood flow and shear stress

When the BFR cuff is inflated around the limb, different levels of the vascular tree are subjected to altered blood flow profiles. Venous blood pressure is typically <5 mmHg at rest and increases to 8–12 mmHg during dynamic exercise (Rådegran & Saltin, 1998). Therefore, even the relatively low cuff pressures used in most BFR exercise studies (~80–120 mmHg) result in venous occlusion, increased venous pressure distal to the cuff, reduced distal perfusion pressure and decreased capillary and resistance vessel flow (Hudlicka & Brown, 2009). Within conduit arteries at rest, there is a gradual decrease in blood flow as cuff pressure increases, with complete occlusion of the brachial and popliteal arteries occurring at pressures >120 and >150 mmHg, respectively (Hunt et al., 2016). Higher pressures are required for complete occlusion of the femoral artery. For example, a cuff pressure of ~180 mmHg elicited a 40–80 and 50–70% reduction in femoral arterial blood flow (measured proximally to the bifurcation) at rest and during submaximal knee-extensor exercise, respectively, compared with exercise without BFR at the same absolute work rate (Christiansen et al., 2019b). Alterations in the shear stress pattern in conduit arteries invoked by BFR (80 mmHg) are demonstrated by an increase in retrograde shear rate during isometric handgrip exercise [at 60% of maximal voluntary contraction] and an accompanying reduction in anterograde shear rate (Credeur et al., 2010). More moderate levels of BFR (~60 mmHg) can completely attenuate exercise-induced

anterograde shear stress (Tinken et al., 2010), although the effect of BFR exercise on remote sites of the peripheral vasculature, where retrograde shear stress could increase (Green et al., 2002), are not fully known. Upon cuff deflation after BFR exercise, all vessels are exposed to a substantial increase in the rate of blood flow (reactive hyperaemia), which can increase more than 3-fold relative to that observed after intensity-matched exercise without BFR (Christiansen et al., 2019b; Takarada et al., 2000). The increase in blood flow can be maintained up to 1 h after deflation (Gundermann et al., 2012), which is likely to sustain the anterograde shear stress stimulus.

6.2 | Skeletal muscle oxygenation and hypoxia

Given the reduction in skeletal muscle blood flow, muscle oxygen saturation is reduced in a manner proportionate to the level of BFR (Karabulut et al., 2011). In several studies, reduced muscle oxygenation, assessed using near-infrared spectroscopy, has been observed during low-load resistance exercise or low-intensity cycling with BFR to levels equal to, or even lower, than that achieved during higher-load/intensity exercise in normal blood flow conditions (Corvino et al., 2017; Downs et al., 2014). Christiansen et al. (2019b) demonstrated that the levels of muscle hypoxia during interval treadmill running with BFR (cuff pressure ~175 mmHg) were commensurate with those achieved during intensity-matched running in systemic hypoxia with an inspired oxygen fraction of 14% (equivalent to an altitude of ~3250 m above sea level). When BFR is maintained during rest intervals, the reduction in muscle oxygen saturation is sustained (Downs et al., 2014). In all experimental situations, when the BFR cuff was released either between sets or at the end of the exercise bout, the subsequent augmented reactive hyperaemia resulted in a more rapid reoxygenation compared with a non-BFR control.

6.3 | Metabolic stress

Studies using complete circulatory occlusion have shown substantial alterations in skeletal muscle metabolite content after exercise (e.g., Greenhaff et al., 1993; Krustrup et al., 2009). Even during BFR exercise protocols with partial blood flow restriction, significant changes in muscle metabolite content occur during exercise. Although muscle ATP content does not appear to be altered (Christiansen et al., 2018), greater declines in phosphocreatine (~13 mM; Suga et al., 2009) and increases in lactate [~28 mmol (kg dry weight)$^{-1}$; Christiansen et al., 2018] and inorganic phosphate (P_i; ~6 mM; Suga et al., 2009), have been observed in response to low- to moderate-intensity exercise with BFR in comparison to exercise with intact blood flow [phosphocreatine, ~5 mM; lactate, ~10 mmol (kg dry weight)$^{-1}$; P_i, ~1 mM, respectively]. These exacerbated metabolic perturbations have been demonstrated to be of a similar magnitude to those induced by higher-load exercise (Suga et al., 2009, 2010).

6.4 | Reactive oxygen species and oxidative stress

The hypoxic intramuscular environment accompanying BFR exercise provides favourable conditions to generate reactive oxygen species (ROS) (Christiansen, 2019), both in the exercising muscles and in the circulation. Moreover, a second, more potent window for increasing muscle ROS production occurs when the BFR cuff is released in the subsequent recovery period, owing to the marked rise in oxygen availability (Christiansen, 2019). In line with this concept, increases in skeletal muscle markers of ROS accumulation, such as heat shock protein-27, have been observed after a single session of BFR interval running in physically active men (Christiansen et al., 2018). In contrast, direct assessment of mitochondrial bioenergetics in permeabilized muscle fibres has revealed attenuated mitochondrial ROS emission rates 2 h after low-load resistance exercise with BFR (Petrick et al., 2019). However, an earlier elevation (e.g., during and immediately after exercise) in ROS emission rates cannot be excluded. Furthermore, BFR interval training provides more potent protection against excessive cytosolic versus mitochondrial ROS production (Christiansen et al., 2019a), indicating the need to differentiate between ROS sources when assessing the effects of BFR exercise on ROS accumulation.

7 | POTENTIAL FOR AUGMENTING MOLECULAR SIGNALS AND PHYSIOLOGICAL ADAPTATION TO EXERCISE WITH BLOOD FLOW RESTRICTION

The augmented physiological and metabolic stress associated with BFR exercise has the potential to promote the molecular signalling networks and the resultant physiological adaptation beyond what is observed with exercise alone (Figure 4). In this section, we explore this potential of BFR when applied to various types of exercise in relationship to endurance-type adaptations (i.e., capillary growth and mitochondrial biogenesis). For clarity, we make a distinction between low-load resistance exercise (LLRE), low- and moderate-intensity endurance exercise (LI/MI) and sprint interval exercise (SIE). Within each of the following sections, we focus on: (i) primary signals/protein activation; (ii) changes in mRNA content; and (iii) subsequent long-term adaptation.

7.1 | Low-load resistance exercise

Although not typically associated with endurance adaptations, evidence is accumulating that LLRE combined with BFR (Table 1) can enhance endurance-related signalling responses and physiological adaptation.

The assessment of primary signals for angiogenesis and mitochondrial biogenesis has demonstrated a greater phosphorylation of p38MAPK after LLRE [20% of one repetition maximum (1RM)] with BFR in comparison to work-matched LLRE without BFR (Ferguson et al., 2018). A similar degree of p38MAPK phosphorylation was

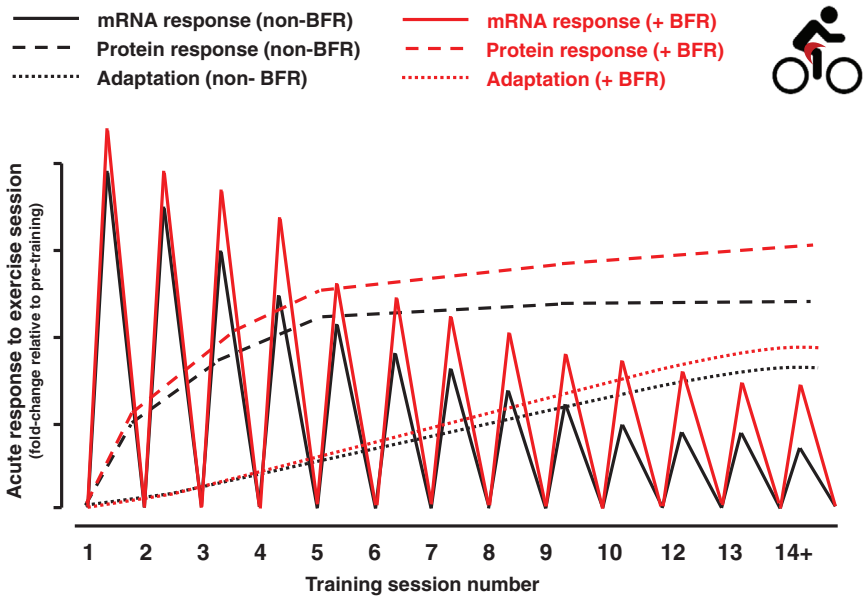

FIGURE 4 Hypothetical schematic diagram of the potential for blood flow restriction (BFR) to augment the molecular signals and associated physiological adaptations with repeated bouts of exercise training. 'mRNA response' represents the acute transcriptional response to single exercise sessions. 'Protein response' represents changes in protein content and/or function (or post-translational modification). 'Adaptation' represents changes in physiological properties associated with capillary growth and mitochondrial biogenesis (mitochondrial content and respiratory function). Black and red lines represent the magnitude and timing of training-induced adaptation in non-BFR conditions (based on Granata et al., 2018) and BFR conditions, respectively

observed after LLRE (30% 1RM) with BFR compared with high-load resistance exercise (HLRE; 70% 1RM; Groennebaek et al., 2018). Although AMPK and CaMKII activity did not change, phosphorylation of acetyl-CoA carboxylase (ACC), a downstream target of AMPK, also increased to a similar extent after LLRE with BFR and HLRE (Groennebaek et al., 2018).

Further work has demonstrated greater increases in the skeletal muscle mRNA content associated with angiogenesis and mitochondrial biogenesis when LLRE is combined with BFR. An enhanced mRNA content of *VEGF*, vascular endothelial growth factor receptor-2 (*VEGFR-2*), *HIF-1α* and neuronal nitric oxide synthase (*nNOS*, *NOS1*) was observed 4 h after LLRE (40% 1RM) with BFR (Larkin et al., 2012). These increases were considerably higher than those elicited by LLRE alone. In the same study, 24 h after exercise, *VEGF*, *VEGFR-2* and *nNOS* mRNA content remained elevated after BFR exercise. Ferguson et al. (2018) made similar observations, with a greater content of *VEGF*, *VEGFR-2*, *HIF-1α*, *eNOS* and *PGC-1α* mRNA after LLRE with BFR in comparison to work-matched LLRE without BFR.

The long-term effects of LLRE training with BFR on capillary growth and mitochondrial adaptations remain to be studied comprehensively. Indirect assessment of microvascular filtration capacity indicates increased skeletal muscle capillarity after LLRE with BFR in healthy men in comparison to work-matched, non-BFR exercise (Evans et al., 2010; Hunt et al., 2013). Recent studies have confirmed that LLRE with BFR increases muscle capillarity. In elite powerlifters, the number of capillaries around type I fibres increased in response to 6.5 weeks of high-frequency (daily) LLRE (~30% 1RM) with BFR, but not after LLRE alone (Bjørnsen et al., 2019). An increase in capillary-to-fibre ratio (C:F; ~23%) and capillary area (~30%) in response to 3 weeks of high-frequency (one or two daily sessions) LLRE (20% 1RM) was observed with BFR performed to volitional failure, in comparison to work-matched, non-BFR exercise (Nielsen et al., 2020). These adaptations occurred alongside a proportional increase in muscle fibre area (Nielsen et al., 2012), resulting in a stable capillary density (number of capillaries per unit cross-sectional area of muscle). The increases in capillarity in response to short-term (~3 weeks) BFR training are striking, because longer periods (4–6 weeks) of training are typically required to increase skeletal muscle capillary supply (Klausen et al., 1981). Muscle capillary supply also increases after a longer BFR training intervention with a lower training frequency. The number of capillaries in contact with type I muscle fibres increased after 6 weeks (three sessions per week) of LLRE (30% 1RM) with BFR performed to volitional failure (Pignanelli et al., 2020). Although similar changes were also observed after LLRE training without BFR (also performed to volitional failure), the training volume was ~33% lower in the BFR conditions (Pignanelli et al., 2020), highlighting the potency of BFR exercise. Nevertheless, not all research has demonstrated favourable changes in capillary supply. There was no change in C:F and capillary density in healthy untrained individuals in response to 6 weeks of low-frequency (three sessions per week) training that consisted of bodyweight-loaded squats with BFR (Jakobsgaard et al., 2018). The contrasting results are presumably related to differences in training frequency and volume, cuff occlusion parameters and prior training status.

Mitochondrial adaptations in response to 6 weeks of LLRE (30% 1RM) with BFR were compared with HLRE (70% 1RM) in healthy untrained men (Groennebaek et al., 2018). Mitochondrial biogenesis (assessed by mitochondrial protein fractional synthesis rate using D_2O enrichment) and maximal coupled respiration increased to the same extent with BFR training as with HLRE alone. This indicates that the addition of BFR allows similar adaptations to HLRE at a much lower load, although citrate synthase activity remained unchanged with both interventions in the same study. In contrast, there were no changes in mitochondrial respiratory function after 6 weeks of LLRE with BFR (30% 1RM to volitional failure), despite a significant increase in the non-BFR-trained leg (Pignanelli et al., 2020). However, almost 30% more total work was completed with the non-BFR leg, which might have contributed to greater mitochondrial adaptations in the non-BFR

TABLE 1 Studies investigating skeletal muscle adaptive responses to low-load resistance exercise combined with blood flow restriction

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA and protein expression	
Larkin et al. (2012)	Healthy males and females ($n = 6$) Repeated-measures design	Unilateral knee extension at 40% 1RM, 10 sets of 12 reps BFR: applied throughout exercise, cuff width 5 cm, at 220 mmHg CON: no cuff applied; rep/work matched Muscle biopsies obtained before, 4 and 24 h postexercise		↑ *VEGF* mRNA in BFR (~4-fold) versus CON (no change) at 4 h ↑ *VEGF* mRNA in BFR (~1.5-fold) versus CON (no change) at 24 h → VEGF protein content ↑ *VEGFR-2* mRNA in BFR (~2-fold) versus CON (no change) at 4 h ↑ *VEGFR-2* mRNA in BFR (~1.3-fold) versus CON (no change) at 24 h ↑ *HIF-1α* mRNA in BFR (~1.5-fold) versus CON (no change) at 4 h → *HIF-1α* mRNA at 24 h ↑ *nNOS* mRNA in BFR (~1.5-fold) versus CON (no change) at 4 h ↑ *nNOS* mRNA in BFR (~1-fold) versus CON (no change) at 24 h → *eNOS* and *iNOS* mRNA at 4 h ↑ *iNOS* mRNA in BFR (~1-fold) versus CON (no change) at 24 h→ *eNOS* mRNA at 24 h	
Ferguson et al. (2018)	Healthy, recreationally active males ($n = 6$) Repeated-measures design	Bilateral knee extension at 20% 1RM Four sets of: 1 × 30 reps, 2 × 15 reps, 1 × reps to fatigue BFR: applied throughout exercise, cuff width 13 cm, at 110 mmHg CON: no cuff applied; rep/work matched Muscle biopsies obtained before, 2 and 4 h postexercise	↑ p38MAPK phosphorylation in BFR (~2.3-fold) versus CON (no change) at 2 h → AMPK phosphorylation	↑ *PGC-1α* mRNA in BFR (~6-fold) versus CON (~2-fold) at 2 h ↑ *PGC-1α* mRNA in BFR (~3-fold) versus CON (~1.5-fold) at 4 h → PGC-1α protein content ↑ *VEGF* mRNA in BFR (~5-fold) versus CON (~2-fold) at 2 h ↑ *VEGF* mRNA in BFR (~7-fold) versus CON (~2.5-fold) at 4 h ↑ *VEGFR-2* mRNA in BFR (~5-fold) versus CON (~1.5-fold) at 4 h ↑ *eNOS* mRNA in BFR (~5-fold) versus CON (~2-fold) at 2 h ↑ *eNOS* mRNA in BFR (~4-fold) versus CON (no change) at 4 h ↑ *HIF-1α* mRNA in BFR (~2.5-fold) versus CON (~2-fold) at 2 h	

(Continues)

TABLE 1 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA and protein expression	
Groennebaek et al. (2018)	Healthy, untrained males ($n = 34$) Independent groups design: BFR group $n = 12$, HLRE group $n = 12$, plus a non-exercise control group ($n = 10$)	6 weeks of unilateral knee-extension training: 3 sessions week^{-1} BFR: four sets to failure at 30% 1RM, applied throughout exercise, cuff width 14 cm, at ~79 mmHg (50% of AOP) CON: HLRE: four sets of 12 reps at 70% 1RM Acute study: muscle biopsies obtained before, 0 and 3 h after a single session before training	↔ increase in p38MAPK phosphorylation in BFR (~2.7-fold) and CON (~3.3-fold) at 0 h ↔ increase in ACC phosphorylation in BFR (~2.2-fold) and CON (~2.3-fold) at 0 h → AMPK, CaMKII, CREB and p53 phosphorylation at 0 and 3 h		↔ increase in mitochondrial protein synthesis in BFR (1.19% day^{-1}) and CON (1.15% day^{-1}) ↔ increase in coupled mitochondrial respiration in BFR (38%) and CON (34%) → CS activity
Evans et al. (2010)	Healthy, recreationally active males ($n = 9$) Within-subject bilateral model	4 weeks of bilateral heel-raise training: 3 sessions week^{-1}, four sets of 50 reps BFR: applied to one leg throughout exercise, cuff width 15 cm, at 150 mmHg CON: no cuff applied; rep/work matched			↑ calf filtration capacity in BFR (26%) versus CON (23%; $P = 0.06$)
Hunt et al. (2013)	Healthy, recreationally active males ($n = 11$) Within-subject unilateral model	6 weeks of unilateral plantar flexion: 3 sessions week^{-1}, three sets to failure BFR: applied to one leg throughout exercise, cuff width 13 cm, at 110 mmHg CON: no cuff applied; rep/work matched			↑ calf filtration capacity in BFR (14%) versus CON (no change)
Jakobsgaard et al. (2018)	Healthy untrained males and females ($n = 6$) Single experimental group, no control group	6 weeks of sit-to-stand training: 3 sessions week^{-1} (19 sessions), five sets to voluntary failure BFR: applied throughout exercise, cuff width 10 cm, at 150–180 mmHg No CON group			→ capillary-to-fibre ratio or capillary density → VEGF protein content → protein content of CS, COXIV or β-HAD
Bjørnsen et al. (2019)	Male and female national powerlifters ($n = 17$) Independent groups design: BFR group $n = 9$, CON group $n = 8$	6.5 weeks of periodized strength training: 5 sessions week^{-1}. In weeks 1 and 3, front squat sessions BFR: four sets to failure or 12 and 15 reps at ~30% 1RM; elastic knee bands, applied throughout exercise, cuff width ~14 cm, at ~120 mmHg CON: HLRE, six or seven sets of 1–6 reps at 60–85% 1RM			↑ number of capillaries around type I fibres in BFR (~12%) versus CON (no change) → capillary density of type I and II fibres

(Continues)

TABLE 1 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session: Sensor	Effects of a single exercise session: mRNA and protein expression	Training effects
Pignanelli et al. (2020)	Healthy males ($n = 10$) Within-subject unilateral model	6 weeks of single-leg squat training: 2–3 sessions week^{-1} (16 sessions). Three sets to failure at 30% 1RM BFR: applied to one leg throughout exercise, cuff width 11 cm, at ~153 mmHg (60–70% of LOP) CON: no cuff applied			↔ increase in capillary contacts of type I fibres in BFR (~14%) and CON (~18%) ↔ increase in capillary-to-fibre ratio of type I fibres in BFR (~14%) and CON (~19%) ↑ mitochondrial respiration in CON (~30%) versus BFR (~18%) → protein content of mitochondrial electron transport chain complexes I–V
Nielsen et al. (2020)	Healthy, recreationally active males ($n = 18$) Independent groups design: BFR group $n = 10$, CON group $n = 8$	19 days of unilateral knee-extension training: 1 or 2 sessions day^{-1} (23 sessions), four sets to failure at 20% 1RM BFR: applied throughout exercise, cuff width 13.5 cm, at 100 mmHg CON: no cuff applied; rep/work matched			↑ capillary-to-fibre ratio in BFR (~23%) versus CON (no change) ↑ capillary area in BFR (~30%) versus CON (no change) → capillary density Protein content and mRNA analysed only in BFR group No change in *VEGF* mRNA and protein content Increase in *VEGFR-2* mRNA and protein content Increase in angiopoietin 1 and 2 protein content

↑ indicates greater increase in blood flow restriction compared with the control conditions (e.g., no BFR or HLRE conditions).
↔ indicates no difference in changes between BFR and CON.
→ indicates no change in BFR or CON.
Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, 5′-adenosine monophosphate-activated protein kinase; AOP, arterial occlusion pressure; BFR, blood flow restriction; CaMKII, calmodulin-dependent protein kinase II; CON, control; CREB, cAMP response-element binding protein; CS, citrate synthase; COXIV, cytochrome C oxidase subunit IV; eNOS, endothelial nitric oxide synthase; β-HAD, 3-hydroxyacyl-CoA dehydrogenase; HIF-1α, hypoxia-inducible factor-1α; HLRE, high-load resistance exercise; iNOS, inducible nitric oxide synthase; LOP, limb occlusion pressure; nNOS, neuronal nitric oxide synthase; p38MAPK, p38 mitogen-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1-α; rep or reps, repetitions; 1RM, one repetition maximum; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2.

leg (Granata et al., 2018). Thus, BFR might allow larger mitochondrial adaptations to be gained from LLRE and HLRE only when the total work performed in the control conditions does not exceed that completed in the BFR conditions.

The above studies demonstrate that BFR, when combined with LLRE, can provide an augmented stimulus for increasing muscle capillary supply and mitochondrial biogenesis, despite a reduced training load. Nevertheless, more training studies are required to improve our understanding of how LLRE training with BFR modifies structural changes in the microvasculature and mitochondrial content and function. Work is needed to investigate the effects of overall BFR training volume and to compare work-matched, non-fatiguing regimens with those performed to repetition failure.

7.2 | Low- and moderate-intensity endurance-type exercise

Blood flow restriction has been combined with LI or MI dynamic exercise (Table 2) of various modes (e.g., walking, cycling and

TABLE 2 Studies investigating skeletal muscle adaptive responses to low- and moderate-intensity endurance-type exercise combined with blood flow restriction

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
Norrbom et al. (2011)	Healthy, recreationally active males ($n = 12$) $\dot{V}_{O_2\,max}$ ~51 ml min^{-1} kg^{-1} Repeated-measures design	45 min single-leg knee-extension exercise at 'highest tolerable workload' for duration BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched Muscle biopsies obtained before, 0 and 2 h postexercise	↑ AMPK phosphorylation in BFR (~3-fold) versus CON (~1.5-fold) at 2 h ↔ increase in p38MAPK phosphorylation in BFR (~3-fold) and CON (~3.4-fold) at 0 h	↑ *PGC-1α-a* mRNA in BFR (~7-fold) versus CON (~0.7-fold) at 2 h ↑ *PGC-1α-b* mRNA in BFR (~100-fold) versus CON (~12-fold) at 2 h ↑ total *PGC-1α* mRNA in BFR (~3-fold) versus CON (no change) at 2 h	
Ozaki et al. (2014)	Healthy, recreationally active males ($n = 6$) $\dot{V}_{O_2\,max}$ ~51 ml min^{-1} kg^{-1} Within-subject unilateral model	20 min treadmill walking at 55% $\dot{V}_{O_2\,max}$ BFR: applied to one leg throughout exercise, cuff width 5 cm, ≤240 mmHg CON: no cuff applied; work matched Muscle biopsies obtained before (CON leg only) and 3 h postexercise	↑ p38MAPK phosphorylation in BFR (1.4-fold) versus CON (1.2-fold) at 3 h		
Smiles et al. (2017)	Healthy, untrained males ($n = 9$) $\dot{V}_{O_2\,max}$ ~37 ml min^{-1} kg^{-1} Repeated-measures design	15 min cycling at 40% $\dot{V}_{O_2\,max}$ BFR: applied to one leg throughout exercise, cuff width 18 cm, at ~90 mmHg CON: 30 min cycling at 70% $\dot{V}_{O_2\,max}$, no cuff applied Muscle biopsies obtained at rest 2 weeks before (as baseline control for subsequent comparisons) and 3 h postexercise	→ p38MAPK phosphorylation		
Christiansen et al. (2018)	Healthy, recreationally active males ($n = 8$) $\dot{V}_{O_2\,max}$ ~58 ml min^{-1} kg^{-1} Repeated-measures design	Three sets of 3 × 2 min treadmill running bouts at 105% lactate threshold (modified D_{max}), each bout interspersed with 1 min and sets with 5 min of active recovery BFR: applied during the running bouts, cuff width 13 cm, at ~175 mmHg, released during recovery period CON: no cuff applied; rep/work matched HYP: normobaric hypoxia (inspired oxygen fraction of 14%, ~3250 m a.s.l.) Muscle biopsies obtained before, 0 and 3 h postexercise	→ αAMPK phosphorylation ↑ ACC phosphorylation in type I fibres in BFR (~3-fold) versus CON (no change) at 0 h ↔ change in CaMKII phosphorylation in type II fibres in BFR and CON at 0 h	↑ total *PGC-1α* mRNA in BFR (~4.3-fold) versus CON (~1.8-fold) at 3 h ↑ *PGC-1α1* mRNA in BFR (~2.3-fold) versus CON (~1.2-fold) at 3 h ↑ *PGC-1α4* mRNA in BFR (6-fold) versus CON (~2-fold) at 3 h → *PGC-1α* mRNA in HYP	

(Continues)

TABLE 2 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
Preobrazenski et al. (2020)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~43 ml min^{-1} kg^{-1} Repeated-measures design	30 min cycling exercise at ~OBLA (4 mmol l^{-1}) BFR: cycling performed supine with legs above the heart CON: cycling performed upright with legs below the heart, work-rate matched Muscle biopsies obtained before, 0 and 3 h postexercise	↑ ACC phosphorylation in BFR (~3-fold) versus CON (~2-fold) at 0 h ↔ increase p38MAPK phosphorylation in BFR (~1.5-fold) and CON (~2-fold) at 0 h	↑ *PGC-1α* mRNA in BFR (~6-fold) versus CON (~4-fold) at 3 h ↔ increase in *VEGF-A* mRNA in BFR (~2.8-fold) and CON (~2.4-fold) at 3 h → increase in *HIF-1α* mRNA	
Gustafsson et al. (1999)	Healthy, recreationally active males ($n = 15$) Repeated-measures design	45 min single-leg knee-extension exercise, at ~25% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched Muscle biopsies obtained before and 30 min postexercise		↔ increase in *VEGF* mRNA in BFR (236%; $P = 0.1$) and CON (111%) at 30 min → *HIF-1α* mRNA	
Gustafsson et al. (2005)	Healthy, recreationally active males ($n = 9$) Repeated-measures design	45 min single-leg knee-extension exercise, at ~25% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched Muscle biopsies obtained before, 2 and 6 h postexercise		↑ total *VEGF-A* mRNA in BFR (~2.5-fold) versus CON (~1-fold) at 2 h ↑ *VEGF-A_{121}* mRNA in BFR (~2.5-fold) versus CON (~1.3-fold) at 2 h ↑ *VEGF-A_{165}* mRNA in BFR (~3.5-fold) versus CON (~2.2-fold) at 2 h ↑ *VEGF-A_{189}* mRNA in BFR (~3-fold) versus CON (~1.3-fold) at 2 h ↑ *VEGFR-1* mRNA in BFR (~1.5-fold) versus CON (~1-fold) at 2 h ↔ increase in *VEGFR-2* mRNA in BFR (~1.8-fold) and CON (~1.5-fold) at 6 h	
Norrbom et al. (2004)	Healthy, recreationally active males ($n = 9$) Repeated-measures design	45 min single-leg knee-extension exercise, at ~25% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched Muscle biopsies obtained before, 30 min, 2 and 6 h postexercise		↑ *PGC-1α* mRNA in BFR (~7.9-fold) versus CON (~2.4-fold) at 2 h ↑ *PGC-1α* mRNA in BFR (~7.9-fold) versus CON (~2.7-fold) at 6 h	

(Continues)

TABLE 2 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
Conceição et al. (2016)	Healthy, untrained males ($n = 9$) $\dot{V}_{O_2\,max}$ ~37 ml min^{-1} kg^{-1} Repeated-measures design	15 min cycling at 40% $\dot{V}_{O_2\,max}$ BFR: applied to one leg throughout exercise, cuff width 18 cm, at ~90 mmHg CON: 30 min cycling at 70% $\dot{V}_{O_2\,max}$, no cuff applied Muscle biopsies obtained at rest 2 weeks before (as baseline control for subsequent comparisons) and 3 h postexercise		→ *PGC-1α1*, *PGC-1α2*, *PGC-1α3*, *PGC-1α4* and total *PGC-1α1* mRNA	
Gustafsson et al. (2007)	Healthy, recreationally active males ($n = 11$) $\dot{V}_{O_2\,max}$ ~51 ml min^{-1} kg^{-1} Within-subject unilateral model	5 weeks of single-leg knee-extension exercise: 4 sessions week^{-1}, 45 min single-leg knee-extension exercise at 'highest tolerable workload' for duration BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched Muscle biopsies obtained before, and after 10 days and 5 weeks			→ basal *VEGF* or *VEGFR-1* mRNA ↑ basal *VEGFR-2* mRNA in BFR (~3-fold) versus CON (no change) at 5 weeks ↑ basal VEGF protein content in BFR (~3-fold) versus CON (~1.5-fold) at 5 weeks ↑ basal *Ki67* mRNA in BFR (~35-fold) versus CON (~8-fold) at 5 weeks
Kaijser et al. (1990)	Healthy, recreationally active males ($n = 8$) Within-subject unilateral model	4 weeks of single-leg training on cycle ergometer: 4 sessions week^{-1}, 45 min at ~45% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched			↑ CS activity in BFR (25%) versus CON (no change) ↑ PFK activity in BFR only (15%) ↓ LDH activity in BFR (20%)
Esbjornsson et al. (1993)	Healthy, recreationally active males ($n = 8$) Within-subject unilateral model	4 weeks of single-leg training on cycle ergometer: 4 sessions week^{-1}, 45 min at ~45% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched			↑ capillary-to-fibre ratio in BFR → capillary density ↑ CS activity in BFR (no pretraining biopsies; therefore, comparison was made to detraining biopsies)

(Continues)

TABLE 2 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
Christiansen et al. (2019a)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~50 ml min^{-1} kg^{-1} Within-subject unilateral model	6 weeks of interval cycle training: 3 sessions week^{-1}, three sets of 3 × 2 min cycling bouts at 60, 70 and 80% W_{max}, each bout interspersed with 1 min and sets with 5 min of active recovery BFR: applied to one leg during the cycling bouts, cuff width 13 cm, at ~180 mmHg, released during recovery period CON: no cuff applied; work-rate matched			→ VEGF protein content ↑ nNOS protein content in BFR (~18%) versus CON (~11%) ↑ resting AMPK phosphorylation in BFR (~38%) versus CON (~51%; $P = 0.15$) → resting AMPK protein content → resting ACC phosphorylation → resting ACC protein content
Christiansen et al. (2019b)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~50 ml min^{-1} kg^{-1} Within-subject unilateral model	6 weeks of interval cycle training: 3 sessions week^{-1}, three sets of 3 × 2 min cycling bouts at 60, 70 and 80% W_{max}, each bout interspersed with 1 min and sets with 5 min of active recovery BFR: applied to one leg during the cycling bouts, cuff width 13 cm, at ~180 mmHg, released during recovery period CON: no cuff applied; work-rate matched			↑ thigh blood flow during moderate-intensity exercise in BFR (~20%) versus CON (~3%) ↑ thigh blood flow during intense exercise in BFR (~16%) versus CON (~−1%)
Christiansen et al. (2020)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~50 ml min^{-1} kg^{-1} Within-subject unilateral model	6 weeks of interval cycle training: 3 sessions week^{-1}, three sets of 3 × 2 min cycling bouts at 60, 70 and 80% W_{max}, each bout interspersed with 1 min and sets with 5 min of active recovery BFR: applied to one leg during the cycling bouts, cuff width 13 cm, at ~180 mmHg, released during recovery period CON: no cuff applied; work-rate matched			↑ resting femoral artery diameter in BFR (~4%) versus CON (~3%, $P = 0.11$) ↑ thigh O_2 delivery during moderate-intensity exercise in BFR (~23%) versus CON (~4%) ↑ thigh O_2 delivery during intense exercise in BFR (~13%) versus CON (~−1%) ↑ thigh O_2 uptake during moderate-intensity exercise in BFR (~18%) versus CON (~6%)

(Continues)

TABLE 2 (Continued)

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
					→ thigh O_2 uptake during intense exercise → total OXPHOS protein content

↑ indicates greater increase in BFR compared with the control conditions (e.g., no BFR or high-load resistance exercise conditions).
↔ indicates no difference in changes between BFR and CON.
→ indicates no change in BFR or CON.
Abbreviations: ACC, acetyl-CoA carboxylase; AMPK, 5' adenosine monophosphate-activated protein kinase; BFR, blood flow restriction; CaMKII, calmodulin-dependent protein kinase II; CON, control; CS, citrate synthase; Dmax, maximal distance model; FIO_2, inspired oxygen fraction; HIF-1α, hypoxia-inducible factor-1α; HYP, hypoxia; LDH, lactate dehydrogenase; nNOS, neuronal nitric oxide synthase; OBLA, onset of blood lactate accumulation; OXPHOS, oxidative phosphorylation; PFK, phosphofructokinase; p38MAPK, p38 mitogen-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1-α; rep or reps, repetitions; VEGF, vascular endothelial growth factor; VEGFR-1, vascular endothelial growth factor receptor-1; VEGFR-2, vascular endothelial growth factor receptor-2; $\dot{V}_{O_2\,max}$, maximal oxygen uptake; W_{max}, maximum work rate.

running) and types (continuous vs. interval), along with different BFR procedures (intermittent or continuous occlusion, and cuff pressures ranging from ~50 to 240 mmHg).

Several experimental models support that endurance-type exercise with BFR can increase physiological stressors and enhance the activation of molecular signalling networks underlying mitochondrial biogenesis. Greater increases in AMPK activation (as assessed via AMPK or ACC phosphorylation) have been observed after a single session of continuous (Norrbom et al., 2011; Preobrazenski et al., 2020) or intermittent (Christiansen et al., 2018) exercise with BFR, in comparison to work-matched exercise without BFR. In the study by Christiansen et al. (2018), BFR interval exercise elevated ACC phosphorylation in type I but not type II fibres, indicating that some effects of BFR on molecular signalling pathways might be fibre-type specific. It is less clear how BFR exercise affects other signalling pathways related to mitochondrial biogenesis. Increases in p38MAPK phosphorylation have been reported (Norrbom et al., 2011; Ozaki et al., 2014; Preobrazenski et al., 2020), although similar changes were evident in the non-BFR conditions (Norrbom et al., 2011; Preobrazenski et al., 2020). In contrast, p38MAPK phosphorylation remained unchanged after BFR exercise of a shorter duration (15 vs. 30–45 min) and with a lower intensity (40% of $\dot{V}_{O_2\,max}$; Smiles et al., 2017). These contrasting findings might be explained by differences in exercise duration and intensity, BFR parameters or the timing of muscle biopsies. In addition, CaMKII phosphorylation was lowered to the same extent after a session of interval exercise with or without BFR, but not when the session was performed in normobaric systemic hypoxia (Christiansen et al., 2018), suggesting that Ca^{2+}-related signalling through CaMKII, when assessed at exercise termination, is not augmented by BFR exercise.

Consistent with the stimulating effect of BFR exercise on AMPK and its role in inducing mRNAs associated with mitochondrial biogenesis, *PGC-1α* mRNA content increased more after various types of BFR exercise compared with work-matched exercise without BFR, including single-leg knee-extension exercise (Norrbom et al., 2004, 2011), intermittent running (Christiansen et al., 2018) and cycling (Preobrazenski et al., 2020). Indeed, when the same intermittent running protocol was performed during systemic hypoxia (inspired oxygen fraction of 14%), there was no increase in *PGC-1α* mRNA (Christiansen et al., 2018), suggesting that the enhanced signalling with BFR was unrelated to the absolute level of skeletal muscle hypoxia. In contrast, no increases in *PGC-1α* mRNA content were observed after low-intensity cycling with BFR (15 min, 40% $\dot{V}_{O_2\,max}$; Conceição et al., 2016), which might be explained, at least in part, by the short duration and low intensity of exercise. Furthermore, Conceição et al. (2016) did not include work- and duration-matched control conditions, which complicates the interpretation of their results further.

Despite the potential for LI/MI exercise with BFR to promote indicators of mitochondrial biogenesis, few studies have explored the long-term effects of BFR training on mitochondrial content and respiratory function. Early work by Kaijser et al. (1990) and Esbjörnsson et al. (1993) showed that citrate synthase activity was higher in a BFR-trained leg (using the hyperbaric method) compared with a non-BFR control leg. In agreement, Christiansen et al. (2020) recently showed that BFR interval training, in contrast to a work-matched training control, increased the leg diffusional O_2 conductance during isolated knee-extensor exercise. Given that convective O_2 delivery does not pose a limitation to O_2 uptake by contracting muscles with this exercise model, this suggests an improvement in muscle mitochondrial function. In the same study, there was a dissociation between adaptations in leg O_2 delivery/uptake and those of mitochondrial protein (OXPHOS) abundance (the latter did not change). Thus, although BFR interval training increases the potential of the leg to use O_2 for ATP generation, this is not reflected by changes in mitochondrial protein abundance (as assessed by the western blotting technique, which is not necessarily a valid indicator of mitochondrial content; Larsen et al., 2012).

Several studies have investigated how BFR exercise affects angiogenic mRNA content. Initially, no differences were observed between BFR and non-BFR exercise for the increase in *VEGF* mRNA content in skeletal muscle (Gustafsson et al., 1999). In a subsequent study, greater increases in *VEGF* mRNA splice variants (*VEGF-A*$_{121}$, *VEGF-A*$_{165}$ and *VEGF-A*$_{189}$) and *VEGFR-1* mRNA were evident 2 h after BFR exercise compared with the non-BFR control (Gustafsson et al., 2005). The discrepancy between these two studies might be attributable to the timing of the postexercise biopsies, which were obtained only 30 min postexercise in the initial study (Gustafsson et al., 1999), typically before any measurable changes in *VEGF* mRNA content occur (Kuang et al., 2020). More recently, similar increases in *VEGF-A* mRNA content were observed after BFR exercise and the non-BFR control (Preobrazenski et al., 2020). Thus, the effect of a single session of BFR exercise on *VEGF* mRNA content remains unclear.

Longitudinal studies have explored the effect of LI/MI training with BFR on protein markers of angiogenesis. A greater increase in the resting muscle abundance of VEGF-A protein was reported after 5 weeks of continuous BFR training compared with a training control (Gustafsson et al., 2007). Furthermore, the basal level of *Ki67* mRNA increased more in the BFR-trained leg (Gustafsson et al., 2007). In contrast, muscle VEGF protein abundance remained unaltered after 6 weeks of interval cycling with BFR (Christiansen et al., 2019a). The contrasting findings for VEGF protein might be attributed to differences in the exercise training protocols. However, the selective increases in leg blood flow (Christiansen et al., 2019b) and oxygen delivery and uptake (Christiansen et al., 2020) during single-leg exercise for the BFR-trained leg indicates that a microvascular adaptive response had taken place early during the intervention. Indeed, although capillary supply was not assessed (Christiansen et al., 2020), the classic studies of Sundberg and colleagues had already established the potential of LI/MI exercise training with BFR to increase muscle capillary density (Esbjörnsson et al., 1993).

Overall, the present data indicate that LI/MI BFR exercise can invoke a greater stimulation of endurance-type adaptations than absolute intensity-matched exercise without BFR. To elaborate on the potency of LI/MI BFR exercise for promoting endurance-type adaptations, future studies should incorporate a high-intensity exercise control. Furthermore, the findings above also underscore that although mRNA and protein measurements can provide interesting insights about the potential of a training strategy for increasing endurance-type adaptations, they do not necessarily reflect adaptations in muscle functional properties (e.g., blood perfusion, O_2 delivery and mitochondrial function) at a given point in time. Further research is warranted to confirm and expand these initial observations, particularly in cohorts of endurance athletes.

7.3 | Sprint interval exercise

Although the combination of BFR with LI/MI exercise augments some of the acute signals and long-term physiological adaptations associated with endurance performance, the maintenance of a high training intensity is considered important to optimize adaptations and performance in trained athletes (Laursen et al., 2005). To date, only two studies have investigated the effect of a single session of SIE with BFR (Table 3). In one of these studies, Taylor et al. (2016) used an SIE protocol on trained participants ($\dot{V}_{O_2\,max}$ ~60 ml min^{-1} kg^{-1}), which consisted of repeated, maximal 30 s sprints separated by 4.5 min of recovery, during which BFR (~130 mmHg) was rapidly applied and maintained for 2 min. The addition of BFR did not augment the increase in AMPK phosphorylation immediately after the exercise session (Taylor et al., 2016). Consistent with this finding, there was no further increase in *PGC-1α* mRNA content 3 h after the session, compared with SIE alone (~5- vs. ~6.5-fold, respectively; Taylor et al., 2016). Similar changes in *PGC-1α* mRNA content (~6-fold) have been observed in well-trained cyclists after a session of SIE (Psilander et al., 2010). The lack of effect of BFR in the former study might be attributable to a limited capacity to elicit increases in *PGC-1α* mRNA with intense exercise. Indeed, comparisons of work-matched, high-intensity interval exercise at 73, 100 and 133% of peak work rate demonstrated ~4- to 10-fold increases in *PGC-1α* mRNA 3 h post-exercise, which plateaued at 100% peak work rate, suggesting that supramaximal exercise does not elicit any additional increase in *PGC-1α* mRNA content (Edgett et al., 2013). In contrast to the results for *PGC-1α* mRNA, postexercise BFR resulted in an enhanced content of *HIF-1α* mRNA compared with SIE alone (and a tendency for *eNOS* mRNA to be greater; $P = 0.10$, Cohen's d effect size = 0.72) 3 h postexercise (Taylor et al., 2016).

In a follow-up training study, angiogenic and mitochondrial adaptations to 4 weeks of sprint interval training (SIT) with or without postexercise BFR were assessed in trained individuals ($\dot{V}_{O_2\,max}$ of ~63 ml min^{-1} kg^{-1}; Mitchell et al., 2019). Co-localization of Ki67 with CD31$^+$ cells (a marker of endothelial cell proliferation), demonstrated a near significant interaction effect ($P = 0.06$; Cohen's d effect size = 0.63), indicating that endothelial cell proliferation might increase with SIT plus BFR in trained subjects (Mitchell et al., 2019). This adaptation often precedes any measurable changes in skeletal muscle capillary supply (Høier et al., 2010, 2020). However, there was no increase in any index of skeletal muscle capillarity (capillary density, capillary-to-fibre ratio and capillary–fibre contacts). Moreover, citrate synthase, COXII and COXIV protein abundance remained unchanged (Mitchell et al., 2019).

Although shear stress was likely to be high during SIE with post-exercise BFR, the accumulated shear stress stimulus might have been lower than that invoked by the continuous, moderate-intensity exercise protocols discussed in the previous section, owing to the lower overall training volume (Høier et al., 2013). Thus, the insufficient training volume and an attenuated BFR-induced shear stress stimulus could explain the absence of changes in capillary markers in the study by Mitchell et al. (2019). Another explanation might be the high training status of the participants, in whom the resting muscle C:F ratio (~2.9) was almost double that of the untrained participants (~1.6) in a 6 week SIT study that induced a ~30% increase in C:F ratio (Cocks et al., 2013).

TABLE 3 Studies investigating skeletal muscle adaptive responses to sprint interval exercise combined with blood flow restriction

Study	Participants and study design	Methods	Effects of a single exercise session		Training effects
			Sensor	mRNA expression	
Taylor et al. (2016)	Trained males ($n = 8$) $\dot{V}_{O_2\ max}$ ~60 ml min^{-1} kg^{-1} Repeated-measures design (acute study)	4 reps of maximal 30 s sprints on a cycle ergometer, interspersed with 4.5 min of supine rest BFR: applied immediately post-sprint for 2 min, cuff width 12 cm, at ~130 mmHg CON: no cuff applied; rep/work matched Muscle biopsies obtained before, 0 and and 3 h postexercise	↔ increase p38MAPK phosphorylation in BFR (~4.1-fold) and CON (~3.2-fold) at 0 h	↔ increase *PGC-1α* mRNA in BFR (~6.5-fold) and CON (~5-fold) at 3 h ↔ increase *VEGF* mRNA in BFR (~3-fold) and CON (~2.5-fold) at 3 h ↔ increase *VEGFR-2* mRNA in BFR (~2.3-fold) and CON (~1.4-fold) at 3 h ↑ *HIF-1α* mRNA in BFR (~1.5-fold) versus CON (no change) at 3 h → *eNOS* mRNA in BFR (~1.7-fold; $P = 0.10$) versus CON (no change) at 3 h → *MMP-9* and *Ang-2* mRNA	
Mitchell et al. (2019)	Trained males ($n = 21$) $\dot{V}_{O_2\ max}$ ~63 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 11$, CON group $n = 10$	4 weeks of SIT: 2 sessions week^{-1}, 4–7 reps of maximal 30 s sprints on a cycle ergometer, interspersed with 4.5 min of supine rest BFR: applied immediately post-sprint for 2 min, cuff width 12 cm, at ~130 mmHg CON: no cuff applied; rep/work matched			→ capillary contacts, capillary-to-fibre ratio or capillary density → Ki67$^+$ (proliferating) endothelial cells (interaction: $P = 0.06$) → citrate synthase, COXII and COXIV protein content

↑ indicates greater increase in BFR compared with the control conditions (e.g., no BFR or high-load resistance exercise conditions).
↔ indicates no difference in changes between BFR and CON.
→ indicates no change in BFR or CON.
Abbreviations: Ang-2, angiotensin II; BFR, blood flow restriction; CON, control; COXII, cytochrome C oxidase subunit II; COXIV, cytochrome C oxidase subunit IV; eNOS, endothelial nitric oxide synthase; HIF-1α, hypoxia-inducible factor-1α; MMP-9, matrix metalloproteinase 9; p38MAPK, p38 mitogen-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1-α; rep or reps, repetition; SIT, sprint interval training; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor-2; $\dot{V}_{O_2\ max}$, maximal oxygen uptake.

8 | ENHANCING ENDURANCE PERFORMANCE WITH BLOOD-FLOW-RESTRICTED EXERCISE TRAINING

In the previous sections of this review, we have examined how different types of BFR exercise affect the physiological stressors and some of the molecular signalling networks related to mitochondrial and vascular adaptations that support endurance performance. In this section, we explore how the different types of BFR training (LLRE, LI/MI and SIE) impact endurance-related exercise performance (Table 4).

Kaijser et al. (1990) and Esbjörnsson et al. (1993) made the first observations of an improved endurance exercise performance with BFR training. In these studies, physically active participants completed 4 weeks of single-leg, continuous training with BFR (using the hyperbaric method). Greater improvements in single-leg exercise time to exhaustion in ischaemic conditions were observed after BFR training compared with the control group who performed the same training without BFR. In parallel work by Sundberg et al. (1993), greater improvements in single-leg peak oxygen uptake were achieved with continuous BFR training than with work-matched training without BFR.

Studies of LLRE with BFR have consistently demonstrated enhanced skeletal muscle endurance exercise capacity. In most cases, greater improvements in the number of repetitions performed at a fixed percentage repetition maximal or maximal voluntary contraction have been observed after BFR compared with non-BFR training (e.g., Groennebaek et al., 2018; Kacin & Strazar, 2011; Manimmanakorn et al., 2013). Pignanelli et al. (2020) demonstrated a greater increase in the average power through the mid-portion of a 30-repetition maximal effort muscle endurance task after 6 weeks of single-leg squat training to failure at 30% 1RM with BFR compared with a non-BFR control.

Several studies have also shown that LI/MI training (using various types of exercise) with BFR improves endurance-related performance outcomes. For example, greater improvements in $\dot{V}_{O_2\,max}$ have been found after LI/MI exercise with BFR than after intensity-matched training alone (Abe et al., 2010; de Oliveira et al., 2016), although this is not a universal finding (Kim et al., 2016; Paton et al., 2017). Other indices of endurance performance, such as time to exhaustion (Abe et al., 2010; Christiansen et al., 2019a) and power output during an incremental test (Christiansen et al., 2020; de Oliveira et al., 2016), are also improved in response to this type of BFR training in trained individuals.

Using SIE with postexercise BFR, Taylor et al. (2016) and Mitchell et al. (2019) demonstrated increases in $\dot{V}_{O_2\,max}$ (~5%) in trained cyclists, in contrast to no changes with SIT alone. The increases were evident after only eight training sessions, with a progression in training volume over 4 weeks. However, further work using the same training protocol did not demonstrate any additional enhancement of critical power, as assessed by the power–duration relationship, after BFR training compared with the training control (Mitchell et al., 2019).

9 | CONCLUSIONS AND FUTURE RESEARCH

Exercise with BFR presents an intensified training stimulus (beyond that of performing the same exercise alone) that promotes homeostatic perturbations and associated molecular signalling for endurance adaptation. This greater stimulus appears to induce enhanced physiological adaptations, including increases in muscle capillary supply and mitochondrial function, that can contribute to improvement in endurance-exercise performance.

There is, however, a lack of consensus regarding the potency of BFR training in many of these aspects, which is invariably attributable to the different modes, intensities and durations of exercise and BFR methods. Indeed, effects of BFR training on endurance performance seem to reflect how these variables modulate the molecular signals that govern the underlying physiological adaptations. In addition, the differing training status of participants from the included studies might contribute to the lack of consensus. In many respects, the permutations of intensity and duration of exercise and the application of BFR are endless. More studies are required to elucidate the primary signalling mechanism(s) in response to the various BFR exercise combinations to allow stronger conclusions to be drawn with regard to the best BFR training method for enhancing endurance-type adaptations in the individual athlete. The effectiveness of BFR training on different aspects of athletic performance will also depend on the ultimate goal of the athlete. It should also be appreciated that a benefit of BFR exercise is that multiple physiological systems can be targeted simultaneously or selectively depending on the nature of the BFR protocol.

Based on the present review of the potential for different BFR strategies to enhance endurance adaptation in trained individuals, more studies are still needed to confirm its potential in the endurance athlete. Nevertheless, invasive studies in athletes are rare and are often performed in less trained or sedentary individuals. Moreover, there is a requirement to clarify whether BFR training interventions can be used by high-performance athletes within a broader structured training programme over the course of the athlete's periodized macro- and micro-cycles.

There is a need to develop a better understanding of the minimal BFR training volume required to achieve positive outcomes. Given the high level of physical stress that BFR imparts, particularly when combined with intense interval training, a careful plan for its implementation is required to avoid over-reaching or over-training, where the balance between the adaptive signal and bodily stress needs to be maintained. Moreover, concerns about the safety of BFR exercise have been raised, including the potential risk for muscle damage with very strenuous and unaccustomed BFR resistance exercise (Wernbom et al., 2020). The increased engagement of the exercise pressor reflex, which contributes to the autonomic cardiovascular response to exercise, might also increase the risk for deleterious cardiovascular events (Cristina-Oliveira et al., 2020; Spranger et al., 2015). However, there is evidence that BFR training can reduce this pressor response (Sundblad et al., 2018), modulated either through a reduction in muscle afferent activity or an alteration in central command (Fisher

TABLE 4 Studies investigating exercise performance in response to blood-flow-restricted exercise training

Study	Participants and study design	Method	Performance
Kaijser et al. (1990)	Healthy, recreationally active males ($n = 8$) Within-subject unilateral model	4 weeks of single-leg training on cycle ergometer: 4 sessions week^{-1}, 45 min at highest tolerable workload BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched	↔ increase in single-leg TTE during incremental test performed with normal blood flow in BFR (19%) and CON (15%) ↑ single-leg TTE during incremental test (performed in restricted blood flow conditions) in BFR (25%) versus CON (12%)
Esbjörnsson et al. (1993)	Healthy, recreationally active males ($n = 8$) Within-subject unilateral model	4 weeks of single-leg training on cycle ergometer: 4 sessions week^{-1}, 45 min at ~45% peak work rate BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched	↔ increase in single-leg TTE during incremental test performed with normal blood flow in BFR (19%) and CON (15%) ↑ single-leg TTE during incremental test (performed in restricted blood flow conditions) in BFR (25%) versus CON (12%)
Sundberg et al. (1993)	Healthy, recreationally active males ($n = 10$) Within-subject unilateral model	4 weeks of single-leg training on cycle ergometer: 4 sessions week^{-1}, 45 min at highest tolerable workload BFR: working leg in hyperbaric chamber at pressure 50 mmHg above atmospheric pressure CON: normal atmospheric pressure, work-rate matched	↑ single-leg $\dot{V}_{O_2peak}$ in BFR (24%) versus CON (14%) ↑ single-leg TTE during incremental test in BFR (27%) versus CON (10%)
Abe et al. (2010)	Healthy, recreationally active males ($n = 19$) $\dot{V}_{O_2\,max}$ ~45 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 9$, CON group $n = 10$	8 weeks of cycle ergometer training: 3 sessions week^{-1} at 40% $\dot{V}_{O_2\,max}$ BFR: 15 min exercise, applied throughout exercise, cuff width 5 cm, at ~160–210 mmHg CON: 45 min exercise, no cuff applied	↑ $\dot{V}_{O_2\,max}$ in BFR (6.4%) versus CON (no change) ↑ TTE during maximal incremental test in BFR (15%) versus CON (4%)
Kacin & Strazar (2011)	Healthy, recreationally active males ($n = 10$) Within-subject unilateral model	4 weeks of single-leg knee-extension training: 4 sessions week^{-1} of eight sets of single-leg extension to failure BFR: applied to one leg throughout exercise, cuff width 13 cm, at ~230 mmHg CON: no cuff applied, rep/work matched	↑ number of repetitions performed at 15% MVC in BFR (63%) versus CON (36%)
Manimmanakorn et al. (2013)	Female netball players ($n = 20$) Independent groups design: BFR group $n = 10$, CON group $n = 10$	5 weeks of knee-extension and -flexion RE: 3 sessions week^{-1} of three sets of knee extension and three sets of knee flexion to failure at 20% 1RM BFR: applied throughout exercise, cuff width 5 cm, at ~160–230 mmHg CON: no cuff applied; rep/work matched	↑ number of repetitions at 20% 1RM in BFR (83%) versus CON (62%)
de Oliveira et al. (2016)	Healthy, recreationally active males and females ($n = 37$) $\dot{V}_{O_2\,max}$ ~45 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 10$, CON group $n = 7$, HIT group $n = 10$, HIT + BFR group $n = 10$	4 week of interval cycle training: 3 sessions week^{-1} of two sets of 5–8 reps of 2 min BFR: exercise at 30% of peak power, cuff applied during the bouts, cuff width 18 cm, at 140–200 mmHg, released during recovery period CON: no cuff applied; work-rate matched to BFR exercise HIT: exercise at 95–110% of peak power HIT + BFR: one set was performed as BFR and the other as HIT	↑ $\dot{V}_{O_2\,max}$ in BFR (5.6%), HIT (9.2%) and HIT + BFR (6.5%) versus CON (no change) ↑ power achieved during maximal incremental test in BFR (12%), HIT (15%) and HIT + BFR (11%) versus CON (2%) ↔ increase in OBLA in BFR (16%), HIT (25%) and HIT + BFR (22%) and CON (6%)
Kim et al. (2016)	Healthy, recreationally active males ($n = 31$) $\dot{V}_{O_2\,max}$ ~40 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 11$, CON group $n = 10$, VI group = 10	6 weeks of cycle training: 3 sessions week^{-1}, cycle training BFR: 20 min at 30% heart rate reserve applied throughout exercise, cuff width 5 cm, at 160–180 mmHg CON: no exercise training control VI: 20 min at 60–70% of heart rate reserve	→ in $\dot{V}_{O_2\,max}$

(Continues)

TABLE 4 (Continued)

Study	Participants and study design	Method	Performance
Paton et al. (2017)	Healthy, recreationally active males and females ($n = 16$) $\dot{V}_{O_2\,max}$ ~46 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 8$, CON group $n = 8$	4 weeks of treadmill run training: 2 sessions week^{-1} of two or three sets of 5–8 reps of 30 s running at 80% of peak running velocity BFR: elastic wraps, applied during the running bouts, width 7.5 cm, at a perceived pressure of 7 out of 10, released between each set CON: no wrap applied; work-rate matched	↔ increase in $\dot{V}_{O_2\,max}$ in BFR (6%) and CON (4%) ↑ peak running velocity achieved during maximal incremental test in BFR (4%) versus CON (1%) ↑ TTE at peak running velocity in BFR (27%) versus CON (17%)
Taylor et al. (2016)	Trained males ($n = 20$) $\dot{V}_{O_2\,max}$ ~62 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 10$, CON group $n = 10$ (training study)	4 weeks of SIT: 2 sessions week−1, 4–7 reps of maximal 30 s sprint on a cycle ergometer, interspersed with 4.5 min supine rest BFR: applied immediately post-sprint for 2 min, cuff width 12 cm, at ~130 mmHg CON: no cuff applied; rep/work matched	↑ $\dot{V}_{O_2\,max}$ in BFR (4.5%) versus CON (0.7%) → maximal aerobic power (interaction, $P = 0.09$) → 15 km time trial
Groennebaek et al. (2018)	Healthy, untrained males ($n = 34$) Independent groups design: BFR group $n = 12$, CON group $n = 12$, plus a non-exercise control group ($n = 10$)	6 weeks of unilateral knee-extension training: 3 sessions week^{-1} BFR: four sets to failure at 30% 1RM, applied throughout exercise, cuff width 14 cm, at ~79 mmHg (50% of AOP) CON: HLRE four sets of 12 reps at 70% 1RM	↑ number of repetitions performed at 30% 1RM in BFR (28%) versus CON (not provided)
Christiansen et al. (2019a)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~50 ml min^{-1} kg^{-1} Within-subject unilateral model	6 weeks of interval cycle training: 3 sessions week^{-1}, three sets of 3 × 2 min cycling bouts at 60, 70 and 80% W_{max}, each bout interspersed with 1 min and sets with 5 min of active recovery BFR: applied to one leg during the cycling bouts, cuff width 13 cm, at ~180 mmHg, released during recovery period CON: no cuff applied; work-rate matched	↑ TTE during knee-extension test at 90% of peak power output in BFR (21%) versus CON (10%)
Christiansen et al. (2019b)	Healthy, recreationally active males ($n = 13$) $\dot{V}_{O_2\,max}$ ~50 ml min^{-1} kg^{-1} Within-subject unilateral model	6 weeks of interval cycle training: 3 sessions week^{-1}, three sets of 3 × 2 min cycling bouts at 60, 70 and 80% W_{max}, each bout interspersed with 1 min and sets with 5 min active recovery BFR: applied to one leg during the cycling bouts, cuff width 13 cm, at ~180 mmHg, released during recovery period CON: no cuff applied; work-rate matched	↑ knee-extensor incremental peak power output in BFR (23%) versus CON (11%)
Mitchell et al. (2019)	Trained males ($n = 21$) $\dot{V}_{O_2\,max}$ ~63 ml min^{-1} kg^{-1} Independent groups design: BFR group $n = 11$, CON group $n = 10$	4 weeks of SIT: 2 sessions week^{-1}, 4–7 reps of maximal 30 s sprint on a cycle ergometer, interspersed with 4.5 min supine rest BFR: applied immediately post-sprint for 2 min, cuff width 12 cm, at ~130 mmHg CON: no cuff applied; rep/work matched	↑ $\dot{V}_{O_2\,max}$ in BFR (4.9%) versus CON (no change) ↔ increase in critical power in BFR (3.3%) and CON (3.6%) → maximal aerobic power
Pignanelli et al. (2020)	Healthy males ($n = 10$) Within-subject unilateral model	6 weeks of single-leg squat training: 2 or 3 sessions week^{-1} (16 sessions), three sets to failure at 30% 1RM BFR: applied to one leg throughout exercise, cuff width 11 cm, at ~153 mmHg (60–70% of LOP) CON: no cuff applied	↑ average power output through the mid-portion of a 30-rep maximal effort muscle endurance task in BFR (18%)

↑ indicates greater increase in BFR compared with the control conditions (e.g., no BFR or HLRE conditions).
↔ indicates no difference in changes between BFR and CON.
→ indicates no change in BFR or CON.
Abbreviations: AOP, arterial occlusion pressure; BFR, blood flow restriction; CON, control; HIT, high-intensity training; HLRE, high-load resistance exercise; LOP, limb occlusion pressure; MVC, maximal voluntary contraction; OBLA, onset of blood lactate accumulation; RE, resistance exercise; rep or reps, repetitions; 1RM, one repetition maximum; SIT, sprint-interval training; TTE, time to exhaustion; VI, vigorous intensity; $\dot{V}_{O_2\,max}$, maximal oxygen uptake; $\dot{V}_{O_2peak}$, peak oxygen uptake; W_{max}, maximum work rate.

& White, 1999). Indeed, given the substantial role played by muscle afferent activity for endurance capacity (Amann et al., 2020), any such attenuated feedback after BFR training could contribute to improved performance.

Notwithstanding the safety concerns, the present review supports that BFR exercise may be used to maintain adaptations already gained as a component of tapering phases where the training volume is reduced and the intensity maintained (or increased). Models of BFR training might have applications during specific periods of the athlete's season, for example in rehabilitation after injury, when high mechanical loads are contraindicated. Either way, the potential for BFR exercise to provide 'more bang for buck' for the endurance-trained individual is an exciting prospect that demands further attention.

COMPETING INTERESTS

None declared.

AUTHOR CONTRIBUTIONS

R.A.F. wrote the initial manuscript. All authors critically revised and contributed to the revised manuscript. All authors approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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