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Clinical application and impact of blood-flow-restriction training

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Clinical application and impact of blood-flow-restriction training

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Editorial: Clinical application and impact of blood-flow-restriction training

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KEYWORDS

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Editorial on the Research Topic
Clinical application and impact of blood-flow-restriction training

For a long time, it was firmly believed that a high load in strength training was necessary to achieve muscle mass and strength gains. However, blood flow restriction training has fundamentally challenged this assumption. Numerous studies over the past decades have shown that these biopositive effects can be achieved even with low loads when blood flow to the working muscles is restricted and venous return from the working extremity to the heart is interrupted (Labata-Lezaun et al., 2022; Perera et al., 2022).

This observation is not only a groundbreaking discovery from a muscle physiology perspective but also offers numerous possibilities in the clinical setting from a practical perspective. In this setting, physicians and therapists were often faced with the dilemma that recommendations for preserving or improving musculature through classical strength training with high loads were opposed by the reduced load-bearing capacity of the patients' musculoskeletal system. While BFR training in healthy individuals has been studied extensively in the sports science context, the evidence in the clinical setting is comparatively limited (Hughes et al., 2017). For this reason, the initiation of the Research Topic was an important step in advancing knowledge in this field. The aims and objectives were to expand current knowledge about the feasibility and effects of BFR applications in the clinical setting. This was not only to broaden the range of BFR applications, but also to shed light on possible negative effects of BFR training in patient populations in addition to the positive ones, thus providing a scientific basis for future work.

A total of 35 experts participated in this Research Topic and presented the results from their current investigations. A total of nine studies were accepted to be published in the Research Topic.

Burton and McCormack focus their scoping review on the effects of BFR training on tendon injuries and healthy tendons. They conclude that the limited results to date on this topic are encouraging and that further research in this area is likely merited. Høgsholt et al. also dealt with BFR training and tendons in their work. However, in their feasibility study, the researchers highlighted the effect of BFR training in combination with patient education on gluteal tendinopathy and were able to show that BFR training brought about an improvement in strength and pain. However, the authors also pointed out that they had

one participant who dropped out of the study due to an adverse event in the form of pain below the applied cuff. Even though the affected person was able to resume her daily exercise sessions without the LL-BFR cuff after only 2 weeks, it makes it clear that BFR training can certainly be associated with risks. All the more important are the remarks of Nascimento et al. They point out that a medical history should be taken before starting BFR training to identify such pathologies or comorbidities that could be associated with adverse side effects. For this purpose, they present a model in their publication that could be used in practice.

The studies in this Research Topic have demonstrated that BFR training can be used successfully in a variety of clinical settings. Jørgensen and Mechlenburg report in their case-study that BFR training was able to improve functional performance and reduce swelling in a 17-year old male, suffering from reactive arthritis after a 12-week low load BFR-Training even with low amounts of supervision. In a study by our own research group, we were able to show that BFR training is also a very effective tool in the prehabilitation phase (Franz et al.) Here, too, the patients' load bearing capacity is often reduced and traditional strength training with high loads is unsuitable. After 6 weeks of prehabilitation with BFR prior to total knee arthroplasty implantation, patients' muscle mass, strength, and quality of life (QoL) improved. Cahalin et al. performed a comprehensive literature review on the potential benefits of BFR-Training in heart disease and heart failure. On the basis of current data, BFR training for patients with different cardiac diseases and heart failure not only appears to be safe but also seems to improve numerous parameters, such as left ventricular dysfunction, inflammatory markers, dyspnea, fatigue, and peripheral blood flow. BFR training could also be beneficial for individuals who suffer from sarcopenia preventing them from performing traditional moderate to high load resistance training, or for whom such training would even be associated with an increased risk of injury. Cahalin et al. used a systematic review and meta-analysis to determine whether data have already been published on this topic. Although the authors could not find any studies that explicitly dealt with BFR training in sarcopenia patients, they did find numerous functional improvements in older people, making BFR training interesting for sarcopenia patients. This study highlights the importance of employing inclusion criteria specific to sarcopenia when this is the target population.

As Cuffe et al. showed in a survey-based study of current trends in BFR training, there is a great deal of diversity in the use of BFR training. Not only did users come from different professions, but the equipment used and the training design varied significantly. However, the appropriate devices are indispensable for accurate BFR-application. Citherlet et al. compared two different cuffs and concluded that both failed to accurately modulate blood flow.

We are convinced that the results of this Research Topic will help practitioners and researchers to improve the application of BFR-Training in the clinical setting and to identify relevant research gaps. It is evident, not least from the Research Topic of articles in this Research Topic, that the application of BFR in the clinical setting is an exciting new area of research. However, as a result of its novelty, many questions remain unanswered. Future studies need to shed more light on potential negative side effects, especially in people with pre-existing conditions. Regarding knowledge of the effects of BFR training on the cardiovascular system and passive musculoskeletal system in particular, we are still in our infancy. Even though two of the studies in this Research Topic dealt with the effects on tendon tissue, it must be stated that we still know too little about the effects of BFR training on the passive musculoskeletal system. Also, the possible positive as well as negative effects of BFR training on muscle diseases have not been researched much yet. Furthermore, it is critical that future research implements BFR according to our current understanding of optimal parameters of application (Patterson et al., 2019). Thus, BFR training in the clinical setting remains an interesting Frontier of research.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Effects of Low-Load Blood-Flow Restricted Resistance Training on Functional Capacity and Patient-Reported Outcome in a Young Male Suffering From Reactive Arthritis

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Introduction: Reactive arthritis (ReA) is a chronic inflammatory disease usually caused by a preceding gastrointestinal or genitourinary bacterial infection. ReA usually occurs in the lower limbs causing joint pain and joint swelling. Physiotherapy-led exercise is recommended to prevent muscle atrophy. The purpose of this case report is to describe the outcome after 12 weeks of low-load blood flow restricted resistance training (BFR-RT) as a rehabilitation method for a young male suffering from ReA.

Methods and materials: A 17-year-old male suffered from ReA in the both knee joints and the left hip joint. 36 months after the incident, he suffered from another ReA incident in his right knee. Non-steroid anti-inflammatory drugs and a new arthrocentesis added with corticosteroid injection was unsuccessful in treating the ReA. The patient performed 12 weeks of BFR-RT on the right lower limb with a low amount of supervision after the first week of training. Assessment of unilateral 30-sec chair stand test (u30-sec CST), low-thigh circumference above apex patella, The Knee Injury and Osteoarthritis Outcome Score (KOOS), The Forgotten Knee Joint Score (FJS), and Numeric Ranking Scale for pain (NRS) was performed at baseline and after 3,6,9, and 12 weeks of BFR-RT.

Results: The patient completed all planned exercise sessions. u30-sec CST improved with 7 repetitions (reps) on the right limb and 5 reps on the left leg. Low-thigh circumference decreased 1.1 cm on the right leg and 1.0 on the left leg. KOOS symptoms, ADL, quality of life and FJS demonstrated a clinically relevant change on 10, 14 and 23 points.

Conclusion: The present case study indicates that even with low amounts of supervision BFR-RT could increase functional performance, reduce knee joint swelling and improve key patient-reported outcome.

Keywords: venous occlusion, rehabilitation, exercise training, physical therapy, muscle venous occlusion, muscle

INTRODUCTION

Reactive arthritis (ReA) is a chronic inflammatory disease usually occurring in the lower limb. ReA is often caused by a gastrointestinal or genitourinary bacterial infection which leads to a local immune reaction (Toivanen and Toivanen, 2004; Schmitt, 2017; Wendling et al., 2020). The incidence of ReA after infection varies with an incidence of 1-1.5% after digestive infection and 4-8% after genital Chlamydia infection (Wendling et al., 2020). Further, the duration of ReA-symptoms is normally six to 12 months. Unfortunately, up 30% of all patients suffering from ReA experience chronic arthritic symptoms, and as a part of the treatment, patients with ReA are recommended physiotherapy-led exercise to prevent skeletal muscle atrophy and joint stiffening (Wendling et al., 2020). However, due to the low incidence rate it is practically impossible to perform sufficiently powered randomized controlled trial to determine the most effective exercise modalities for this particular patient population. Therefore, information from smaller-scale studies, such as a case-report can add valuable information to the patient treatment.

Heavy resistance strength training (HRST) with loads corresponding to >75% of the one repetition maximum (1RM) is usually applied to promote skeletal muscle hypertrophy and skeletal muscle strength gains (Garber et al., 2011). HRST has consistently demonstrated to improve both skeletal muscle hypertrophy as well as muscle mechanical function in both healthy adults and patient populations across all age groups (Aagaard et al., 2002; Couppe et al., 2008; Suetta et al., 2008; Vissing et al., 2008; Skoffer et al., 2016; Calatayud et al., 2017; Ferraz et al., 2018). However, due to pain and joint swelling, HRTS may be contraindicated, rendering patients suffering from ReA to search for alternative exercise methods. During the last decade, research on resistance training with loads as low as 20% of 1RM with concurrent partial or complete blood flow restriction to the exercising limb (low-load blood-flow restricted resistance training: BFR-RT) has consistently proven to promote skeletal muscle hypertrophy and increase muscle strength comparable to that of HRTS (Wernbom et al., 2008; Hughes et al., 2017; Grønfeldt et al., 2020). The ability to promote muscle morphological and muscle mechanical adaptations with low loads makes BFR-RT very interesting in clinical rehabilitation (Hughes et al., 2017; Jørgensen et al., 2018, 2020; Petersson et al., 2020). Furthermore, BFR-RT is safe in both cardiac and orthopedic patient populations and leads to greater reduction in knee joint swelling (Hughes et al., 2017, 2019; Groennebaek et al., 2019; Patterson et al., 2019; Jørgensen et al., 2020). Results from our research group have demonstrated that patients can administer BFR exercises safely and correctly with minimal supervision (Petersson et al., 2020, Høghsholt et al., under review). Thus, BFR-RT may be feasible in patients with ReA to maintain or increase skeletal muscle mass and muscle mechanical function without exacerbating joint pain and/or joint swelling.

The purpose of this clinical case report is to describe the outcome after the use of BFR-RT as rehabilitation method for a young male suffering from ReA. We hope this case report will add to the existing literature on physiotherapist-led exercise methods aiming at maintaining and/or increasing functional capacity in patients suffering from ReA.

CASE DESCRIPTION

History

The patient was a formerly healthy 17-year-old young male (weight: 74.5 kg; height: 185 cm. brachial systolic/diastolic blood pressure: 129/78) with no family history of inflammatory joint- or connective tissue diseases. Further, the patient did not suffer from any cardiovascular diseases. After a week of sickness due to a gastrointestinal infection the patient developed ReA in both of his knee joints as well as the left hip joint, hence resulting in hip- and knee joint pain as well as joint swelling, ultimately reducing his physical activity level and quality of life. The ReA of hip joint as well as the knee joints was successfully treated with arthrocentesis, with full recovery in knee joint mobility and only small reduction in hip flexion and hip internal rotation as compared with the right hip joint. At the physical examination at the hospital, the range of motion was not quantified, but only compared between each limb. Thirty-six months after the first ReA, the patient suffered a relapse in his right knee. Similar to the episode, he suffered from knee joint pain and knee joint swelling which resulted in a reduced physical activity-level as well as a reduced quality of life. Treatment with non-steroid anti-inflammatory drugs (NSAID) did not reduce symptoms and a new arthrocentesis and aorticosteroid injection only reduced the knee swelling temporary. After 3 months without improvements, the patient was offered 12 weeks of BFR-RT to (i) improve his functional capacity, (ii) reduce swelling of the knee joint, and (iii) reduce knee symptoms (**Figure 1**). The patient accepted to engage in the study and signed a written informed consent in accordance with the Helsinki Declaration. According to Danish law, case studies do not require formal ethical approval.

Intervention

The BFR-RT was performed at home every second day for 12 weeks, and consisted of squat and lunges (**Figures 2B,C**). The load in each exercise was the body weight. A conically shaped pneumatic cuff (Occlude APS, size: Large, width = 11.7 cm) was placed around the proximal part of the right thigh (**Figure 2A**). Each exercise was performed in 4 sets with 30 repetitions (reps) in round one and 15 reps in round two, three, and four. Each set was interspaced with 30 sec rest and each exercise was separated by a 5-min rest pause. A physiotherapist supervised the exercises during the first week of exercise (**Table 1**). The patient was instructed to apply the cuff correctly, to inflate/deflate the cuff, and check that the inflation was kept constant during the entire duration of each exercise. Also, the patient was carefully instructed in how to perform the exercises correctly. The cuff pressure was an absolute pressure and not determined based on the total limb occlusion pressure. As we decided to maintain a preset repetition scheme (30-15-15-15) and use body weight as load, we decided to gradually increase the cuff pressure with 10 mmHg from week 1 to week 6 (110–150 mmHg). For safety reasons the cuff pressure was kept constant from week 6 to

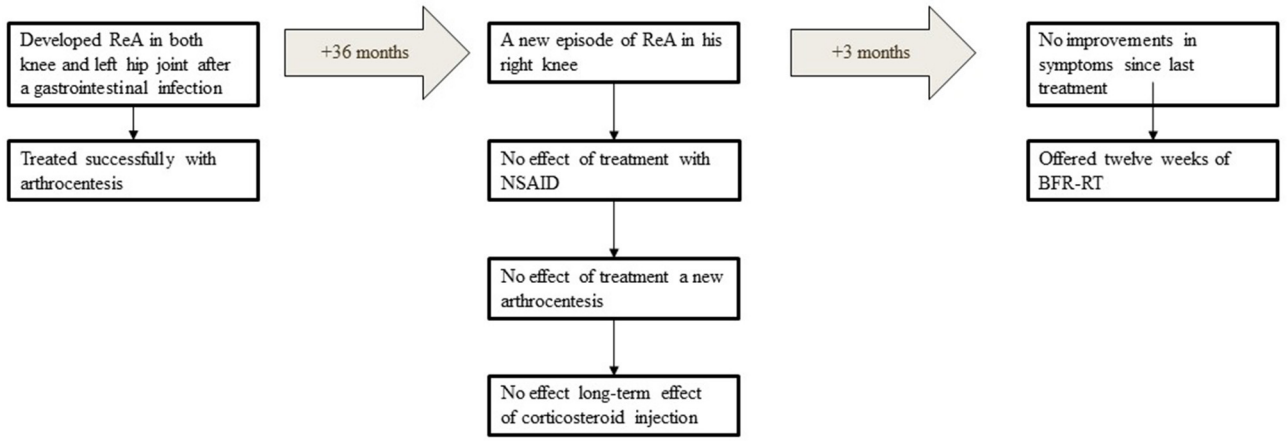

FIGURE 1 | Timeline of the patient history. ReA, reactive arthritis; NSAID, non-steroid anti-flammatory drugs; BFR-RT, blood flow restricted exercise.

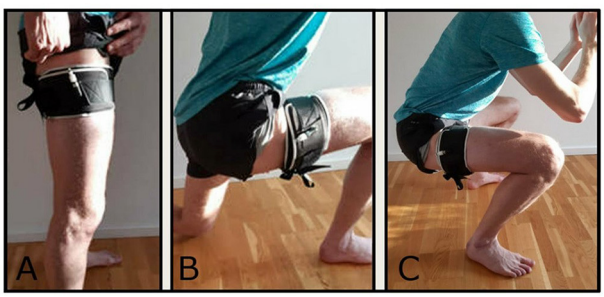

FIGURE 2 | (A) Placement of the pneumatic cuff; **(B)** illustration of the lunge exercise; **(C)** illustration of the squat exercise.

TABLE 1 | Exercise variables.

Exercise variable	
Blood flow restriction	110–150 mmHg
Cuff width	11.7 cm
Sets	4
Load intensity	Body weight
Repetitions 1st set	30
Repetitions 2nd, 3rd, and 4th set	15
Contraction modes per repetition	
Range of motion	Maximum
Rest between sets	30 sec
Rest between exercises	5 mins
Rest between sessions	24 h

week 12. Immediately after the last set of each exercise, the cuff was deflated.

Outcome Measures

One physiotherapist collected outcome measures at baseline and after 3, 6, 9, and 12 weeks of BFR-RT and included unilateral 30-Sec chair-stand test (u30-sec CST) (Thongchoomsin et al., 2020; Waldhelm et al., 2020) and low-thigh circumference with tape measure (Jakobsen et al., 2010) proximal to the upper edge of the patella in standing position. Also, the patient completed the Knee Injury and Osteoarthritis Outcome Score (KOOS) (Roos and Lohmander, 2003) and the Forgotten Knee Joint Score (FJS) (Behrend et al., 2012).

The u30-sec CST is a functional test used to assess lower limb strength (Waldhelm et al., 2020). Before testing, the physiotherapist demonstrated the movement after which the participant performed two practice repetitions to demonstrate the understanding of the test. From sitting on a 45 cm high chair, the patient performed as many single-leg sit to stands with full hip- and knee extension as possible in 30 Sec with the arms crossed in front of the chest. The patient descended until the buttock made contact with the chair. The patient was allowed to reverse the downward-movement as soon as he felt the chair. Thus, he did not have to bear weight through his buttock. Only repetitions correctly performed repetitions (i.e., as described above) were counted. (Waldhelm et al., 2020).

Low-thigh circumference was measured with the patient laying prone on an examination table. To measure low-thigh circumference, a tape measure was placed around the proximal border of the patella while the patient lay relaxed without contraction his knee extensor muscles. A reduction in circumference from baseline to follow-up would represent less joint swelling. Assessing low-thigh circumference with a tape measure has previously been demonstrated to be reliable and reproducible in patients suffering from osteoarthritis (Silva et al., 2014).

The KOOS-questionnaire was completed by the patient prior to the functional tests on each testing day. The patient completed the questionnaire in quiet and undisturbed environment with the possibility to ask the physiotherapist in charge of testing whenever he had questions. The KOOS is a patient-administered knee specific questionnaire comprising five subscales: Pain; Symptoms; Activities of daily living; Sport & Recreation; and Knee-Related Quality of Life. All questions are related to the patients' experiences the last seven days. Each item is scored

TABLE 2 | Outcome measure from baseline to after 12 weeks of BFR-RT.

Outcome measure			Baseline	3 weeks	6 weeks	9 weeks	12 weeks	Absolute difference	% Change
u30-sec CST	Right	reps	10	14	14	14	17	7	41%
u30-sec CST	Left	reps	13	15	15	17	18	4	28%
Low-thigh circumference	Right	cm	41	40.5	40.4	40.4	39.9	1.1	−3%
Low-thigh circumference	Left	cm	38.4	38	37.6	37.8	37.4	1.0	−3%
Knee pain	Right	NRS	0	0	0	0	0		0%
Knee pain	Left	NRS	0	0	0	0	0		0%
KOOS									
Pain		Points	94	94	94	92	94	0	0%
Symptoms		Points	54	54	57	68	64	10	16%
ADL		Points	82	82	93	94	96	14	15%
Sport and recreation		Points	60	70	70	65	65	5	8%
Quality of life		Points	56	69	69	69	69	13	19%
FJS		Points	21	35	44	40	44	23	15%

u30-sec CST, unilateral 30-sec chair stand test; KOOS, Knee Osteoarthritis Outcome Score; FKJS, Forgotten Knee Joint Score; reps, repetitions; cm, centimeters; NRS, Numeric Ranking Scale for Pain.

from 0 to 4 (Roos and Lohmander, 2003). The raw score for each of the five subscales is the total sum of the associated item scores. Scores are transformed to a 0 to 100 scale. The scores of the five subscales are expressed as a composite outcome profile, higher scores indicate fewer problems, and a 10-point change in a subscale score is considered to represent a clinically meaningful change (Nilsdotter et al., 2003; Lyman et al., 2018).

The FJS consists of 12 questions with a five-point Likert response format from 0-4 point (Behrend et al., 2012). The FJS was completed prior to functional performance tests and after completing the KOOS questionnaire on each testing day. As with the KOOS questionnaire, the patient completed the questionnaire in an undisturbed and quiet environment with the possibility to ask the physiotherapist in charge of testing whenever he had questions. The score is transformed into a 0 to 100-point scale with high scores indicating good outcomes (i.e., being less aware of the knee during every day activities) (Behrend et al., 2012, 2017).

The numeric rating scale for pain (NRS) was used to quantify the level of pain prior to each testing session (Hawker et al., 2011). Thus, prior to completing the KOOS questionnaire, the patient reported the level of pain experienced in each knee while sitting relaxed in a chair with ∼90 degree knee flexion on a scale from 0 to 10, where 0 represented no pain at all, and 10 represented the worst imaginable pain (Hawker et al., 2011).

DATA ANALYSIS

Differences from pre- to post-intervention in repetitions, low-thigh circumference, KOOS- and FJS-scores and NRS scores were determined as both absolute change ($post\ score - baseline\ score = absolute\ change$) and relative change in percent ($\frac{post\ score - baseline\ score}{post\ score} \times 100$). Adherence was calculated as $\frac{\frac{Sessions\ completed}{week\ completed}}{session\ scheduled} \times 100 = Adherence$ (%). The statistical analysis was conducted in Stata 17.0 (StataCorp, TX, USA).

The manuscript was written in accordance with the [(Riley et al., 2017)CARE] guidelines.

RESULTS

The participant completed all planned exercise sessions (100% adherence) and all planned outcome assessments sessions (100% adherence).

Pre-to-post improvements in u30-sec CST was demonstrated for both the right and the left lower limb. However, a two-fold relative improvement in lower limb function was observed for the right lower limb (**Table 2**). Low-thigh circumference decreased equally on both the right and left thigh (**Table 2**), while a pain-level corresponding to 0 NRS was maintained throughout the intervention period (**Table 2**).

KOOS subscales Symptoms, Activities of daily living (ADL), and Quality of Life (QOL) displayed a ≥10-point change from baseline to after 12 weeks of BFR-RT. Furthermore, a 23-point reduction in the FJS was demonstrated (**Table 2**).

DISCUSSION

After 12 weeks of BFR-RT every second day, the young male patient suffering from ReA reported and also demonstrated increased functional capacity, a reduction of knee symptoms, increased ability to perform ADL-activities, an improved QOL in line with reducing his awareness of the knee joint after 12 weeks of BFR-RT. Also, 12 weeks of BFR-RT did not provoke additional knee pain or increase knee joint swelling during the exercise period. Therefore, BFR-RT performed as home-based, body weight exercises seems both feasible, safe, and clinically relevant for patients suffering from ReA.

To our best knowledge, this is the first study to demonstrate that 12 weeks of bodyweight BFR-RT every second day was safe and feasible as an exercise method for increasing function and reduce knee joint swelling in a patient suffering from ReA. The reduction in knee swelling was lower than the findings in a RCT performed by Hughes et al. (2019) who reported a 5.8% reduction in knee joint swelling after 12 weeks of BFR-RT in patients with anterior cruciate ligament-reconstruction. However, some of the difference might be due to differences in measuring point as we measured just above the proximal border of the patellar, while Hughes and co-workers measured knee joint swelling at mid-patella level (Hughes et al., 2019). As a similar reduction in knee joint swelling was reported in both knee joints, it seems plausible that the low load applied during exercise (body weight only) was the primary reason for the reduction in knee joint swelling. However, we cannot rule out that the pre-to-post difference is due to test-retest variability. Test-retest variability difference in mid-thigh-circumference has been reported to be -0.3 ± 0.5 cm (Jakobsen et al., 2010), while Hughes et al. (2019) reported a standard error of mean (SEM) was 0.04 cm.

After the intervention period, the patient had improved lower limb function (improved u30-sec CST), suggesting that the exercise method increased lower limb strength and muscular power (Alcazar et al., 2020; Waldhelm et al., 2020). The increased functional performance, measured as an improved unilateral sit-to-stand function, may be due to increased lower limb strength. As such exercising with BFR has been suggested to cause tissue hypoxia, an increment in metabolites, and muscle cell swelling, which all contributes to increased protein synthesis, increased type II muscle fiber recruitment, local and systemic anabolic hormone synthesis, and stimulation of myogenic stem cells (Wernbom et al., 2008; Nielsen et al., 2012; Wernbom and Aagaard, 2019; Vopat et al., 2020). Thus, the gains in muscle strength as a result of exercising, would most likely translate into an improved functional performance. This contrasts the findings in Jakobsgaard et al. (2018) who were unable to find any change in muscle strength in 6 young males after 6 weeks of BFR-RT, although they demonstrated significant improvements in skeletal muscle hypertrophy of the vastus lateralis muscle. However, Yokokawa et al. (2008) demonstrated in a randomized trial increased isometric quadriceps strength and physical function after 8 weeks of BFR-RT with body weight as resistance compared to dynamic balance training in healthy elderly people (Yokokawa et al., 2008). Thus, BFR-RT with body weight can plausibly be considered a valid exercise alternative for increasing skeletal muscle strength in cases where HRST are contraindicated or impossible due to external circumstances (i.e., COVID-19 social restriction).

Importantly, despite exercising every second day for 12 weeks, these improvements were attained without inducing knee pain or increasing knee joint swelling indicating that present BFR-RT protocol was tolerable without overloading the knee joint and the surrounding structures.

Three of 5 KOOS subscales improved with at least 10 point and FJS improved 23 point after 12 weeks of BFR-RT also indicating that the patient benefitted from the BFR-RT protocol. This is in line with other studies utilizing BFR as an exercise treatment (Tennent et al., 2017; Ferraz et al., 2018). Ferraz et al. conducted a three-armed RCT presented demonstrated an pre-to-post improvement in all WOMAC subscales after 12 weeks of BFR-RT in patients suffering from knee OA (Ferraz et al., 2018). Also, Tennent et al. (2017) performed a pilot RCT and found significant improvements in all KOOS subscales after 12 sessions of postoperative BFR-RT in younger patients recovering from non-reconstructive arthroscopy (Tennent et al., 2017). Thus, based on the findings in our case study as well as findings from the above mentioned studies, it seems plausible that BFR-RT can induce functional improvements and increase patient-reported outcomes.

Limitations

Some limitation to the present study needs to be addressed. The inherent limitations of a case report with only one participant renders any firm conclusions on the efficacy of the exercise method. However, due to the low prevalence of ReA it can be difficult to include several participants. Therefore, we consider the present case report important to both (i) demonstrate that BFR-RT was feasible as home-based exercise rehabilitation and (ii) improved functional performance and patient-reported outcomes. Furthermore, the exercise protocol utilized in the present study withholds some limitations that needs to be addressed. First, we decided to include a bilateral exercise (squat) while only restriction blood flow to the right lower limb. As the BFR accelerates the fatigue during an exercise compared to performing the same exercise without BFR (Counts et al., 2016; Loenneke et al., 2017; Jessee et al., 2018; Mattocks et al., 2018), the free-flow limb may compensate for the BFR-limb as it fatigues during the exercise. Therefore, we do know the extent the BFR-limb reached a true fatiguing state. To our best knowledge, the application of unilateral BFR during a bilateral exercise has only been performed in a few studies (Kilgas et al., 2019; Høghsholt et al., under review), both of which demonstrated improved functional performance after 8 weeks of exercise. Secondly, we used an absolute pressure to restrict blood flow to the exercising limb which gradually increased from 110 mmHg to 150 mmHg during the first 6 weeks of exercise. As we decided to utilize a preset repetition scheme while not adding any external load during the exercise period, we decided to restrict the blood flow gradually to increase the intensity of the exercise. This is in line with a previous study by Jakobsgaard et al. (2018) who utilized body weight sit to stand with BFR in healthy young males, increased the blood flow restriction during the intervention period (from 100 to 150–180 mmHg) to decrease the number of repetitions performed in each session. Additionally, Dankel et al. (2017), found that higher BFR pressures increased fatigue verified as decrements elbow flexor torque at very low loads (10–20% 1RM) without any differences in total training volume (load $\times$ repetitions). Thus, based on both Dankel et al.

(2017) and Jakobsgaard et al. (2018) we wanted to utilize BFR pressure to increase the exercise intensity rather than adding external load to the exercises. Thirdly, as we used an absolute BFR pressure, we do not know if the applied pressure is within the recommended recently recommended range of 40–80% of total limb occlusion pressure (Patterson et al., 2019). To increase safety of prescribing BFR-RT as a home-based exercise method, we would recommend future studies to apply a relative pressure. However, similar absolute pressures have previously been applied in healthy young people with reporting any adverse events (Nielsen et al., 2012; Jakobsgaard et al., 2018). Therefore, we considered the present exercise protocol as safe to perform as a home-based rehabilitation program.

Clinical Application

The exercise protocol applied in the present study demonstrated to be feasible and safe in this particular patient. Furthermore, the patient was able to perform the protocol at home without daily supervision, hence rendering the necessity for frequent inpatient visits. Thus, with relatively few supervised sessions, BFR-RT can be considered a clinically relevant exercise method for patients in need of rehabilitation to increase muscle function.

In conclusion, the present study indicates that BFR-RT can be performed safely with high adherence in patients suffering from ReA to increase functional performance, reduce knee joint swelling, and improve patient-reported outcomes. Future studies are required to compare the present exercise protocol performed with and without BFR to determine the necessity of BFR during these body weight exercises.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

IM: contributed to conception, design of the study, organized the database, and wrote sections of the manuscript. SJ: performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REVIEW
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A Useful Blood Flow Restriction Training Risk Stratification for Exercise and Rehabilitation

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Blood flow restriction training (BFRT) is a modality with growing interest in the last decade and has been recognized as a critical tool in rehabilitation medicine, athletic and clinical populations. Besides its potential for positive benefits, BFRT has the capability to induce adverse responses. BFRT may evoke increased blood pressure, abnormal cardiovascular responses and impact vascular health. Furthermore, some important concerns with the use of BFRT exists for individuals with established cardiovascular disease (e.g., hypertension, diabetes mellitus, and chronic kidney disease patients). In addition, considering the potential risks of thrombosis promoted by BFRT in medically compromised populations, BFRT use warrants caution for patients that already display impaired blood coagulability, loss of antithrombotic mechanisms in the vessel wall, and stasis caused by immobility (e.g., COVID-19 patients, diabetes mellitus, hypertension, chronic kidney disease, cardiovascular disease, orthopedic post-surgery, anabolic steroid and ergogenic substance users, rheumatoid arthritis, and pregnant/postpartum women). To avoid untoward outcomes and ensure that BFRT is properly used, efficacy endpoints such as a questionnaire for risk stratification involving a review of the patient's medical history, signs, and symptoms indicative of underlying pathology is strongly advised. Here we present a model for BFRT pre-participation screening to theoretically reduce risk by excluding people with comorbidities or medically complex histories that could unnecessarily heighten intra- and/or post-exercise occurrence of adverse events. We propose this risk stratification tool as a framework to allow clinicians to use their knowledge, skills and expertise to assess and manage any risks related to the delivery of an appropriate BFRT exercise program. The questionnaires for risk stratification are adapted to guide clinicians for the referral, assessment, and suggestion of other modalities/approaches if/when necessary. Finally, the risk stratification might serve as a guideline for clinical protocols and future randomized controlled trial studies.

Keywords: blood flow restriction, risk assessment, risk factors, kaatsu, assessment

INTRODUCTION

Blood flow restriction training (BFRT) has been recognized as a critical tool in rehabilitation medicine, athletic and clinical populations. Although increases in muscle strength following high load resistance training (RT) appear significantly greater than low load RT with BFR, BFR induces similar hypertrophy and lower joint forces/stress with low load RT compared to high load traditional RT without BFR (Bagley et al., 2015; Scott et al., 2016; Hughes et al., 2017; Centner et al., 2019; Rolnick and Schoenfeld, 2020a). Besides the potential implementation of BFRT in clinical musculoskeletal rehabilitation (e.g., knee osteoarthritis, and anterior cruciate ligament reconstruction) (Hughes et al., 2017), clinicians prescribing BFRT are often faced with the BFRT paradox: while participation in regular BFRT (e.g., aerobic training, resistance training, and passively without exercise) is acknowledged to offer significant benefits in muscle mass and strength, it can possibly result in adverse events (e.g., numbness, nausea, hypertension, headache, venous thrombus, deterioration of ischemic heart disease, fainting, tingling, excessive pain, central retinal vein occlusion, and rhabdomyolysis) if applied inappropriately (Nakajima et al., 2006; Ozawa et al., 2015; Noto et al., 2017; Yasuda et al., 2017; Patterson and Brandner, 2018; de Queiros et al., 2021). Such occurrences are very infrequent but have been previously documented.

As the use of BFRT continues to expand in clinical practice, the available literature does not definitively answer if the positive health outcomes outweigh the risks of adverse signs, symptoms, or events during or after exercise with BFR. Nonetheless, despite the beneficial adaptations to skeletal muscle, little is known about long-term changes to vascular health and hemodynamics (Wong et al., 2021). This is important as most studies have stringent inclusion/exclusion criteria, leaving limited data on individuals with comorbidities frequently seen in rehabilitation clinics (Severin et al., 2020).

Despite the desirable effects on skeletal muscle function, BFRT may evoke increased blood pressure and abnormal cardiovascular responses secondary to the augmented and sustained activation of the muscle metaboreflex (Spranger et al., 2015; Cristina-Oliveira et al., 2020). Furthermore, some important concerns with the use of BFRT exists for individuals with established cardiovascular disease (e.g., hypertension, diabetes mellitus, and chronic kidney disease patients), as even appropriate use of BFRT could lead to clinical deterioration of vascular health caused by increased retrograde shear stress, intermittent sympathetic overactivity, and blood pressure elevation (Domingos and Polito, 2018; Wong et al., 2018; da Cunha Nascimento et al., 2020a,b). Thus, these potential adverse outcomes do not support the general claims about safety of BFRT for medically compromised populations (e.g., chronic disease and under cardiac rehabilitation) (Spranger et al., 2015; Cristina-Oliveira et al., 2020).

Conversely, considering the risks of thrombosis promoted by BFRT, a recent systematic review demonstrated that BFR exercise does not exacerbate the activation of coagulation nor enhance fibrinolytic activity (Nascimento et al., 2019). However, it isn't easy to advocate that BFRT is innocuous due to the state of the current literature from the heterogeneity of applied BFRT protocols. BFRT should be prescribed with caution, especially for medically compromised populations or those with increased risk of clotting (e.g., anabolic agents).

To avoid untoward outcomes and ensure that BFR exercise is properly used according to current best practice guidelines, efficacy endpoints such as a questionnaire for risk stratification involving a review of the patient's medical history, signs, and symptoms indicative of underlying pathology is strongly advised. A recent review paper reported that a significant barrier to successful BFRT implementation includes difficulty with integrating a comprehensive and systematic medical screening process, and determining when it is best to include BFRT into a plan of care while considering relevant participant characteristics like pain, loading intolerances, clotting issues, hemodynamics, and recent physical activity history (Rolnick et al., 2021). The proposed model aimed to improve the provision of best practice BFRT prescription for people across the health spectrum by utilizing a thorough screening process. However, the screening approach did not mention specific medical diagnoses frequently encountered in clinical practice and instead focused on encouraging pertinent thought processes likely to minimize risk when applying BFRT in medically compromised populations. Therefore, the proposed approach lacks specificity in assigning relative safety risk profiles to medically compromised populations commonly seen in outpatient rehabilitation and thus the assessment of risk is still primarily left to clinician opinion.

Evaluation of the individual patient for BFRT represents a potentially complex medical screening problem. A list of individual risk factors that are associated with adverse responses to BFRT has already been discussed and proposed elsewhere to aid in the screening process (Nakajima et al., 2011; Kacin et al., 2015; Brandner et al., 2018; Bond et al., 2019; Rolnick et al., 2021). However, a considerable amount of information regarding their impact on health is scattered throughout the literature and not compiled in a BFR-specific resource. A screening tool that considers the available evidence on BFRT that relies on a comprehensive personal, medical, and family history will assist clinicians in proposing the best management strategy for an individual patient with a given condition. We believe this approach will minimize the risk of adverse events while maximizing health benefits during BFRT.

Therefore, the overall aim of this manuscript is to provide a potentially useful BFRT questionnaire for risk stratification for exercise and rehabilitation. We review the primary adverse and beneficial effects of BFRT for healthy individuals and populations with chronic disease including hypertension, cardiovascular disease, rheumatoid arthritis, diabetes mellitus, and chronic kidney disease as well as assessing potential risks in patients following COVID-19 infection, post-surgery, those who are pregnant or postpartum and individuals with or without use of anabolic steroids, and ergogenic substances. Furthermore, we provide additional insights into the application, effectiveness, and utilization of BFRT for different populations while discussing future directions that warrant consideration in basic and clinical studies. These reports have high relevance in the field of exercise

physiology and sports medicine as BFRT is a rapidly growing modality in fitness and rehabilitation settings.

DEVELOPING A RISK ASSESSMENT TOOL IN CHRONIC DISEASE

Clinicians are encouraged to consider this risk stratification when exercising their judgment in determining and implementing BFRT with their patients. This pre-screening tool does not supersede the responsibility to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with the patient and their referring physician and/or other members of their healthcare team.

A questionnaire for risk stratification to BFRT can theoretically optimize safety and mitigate risk. We recommend considering the patient's baseline health status and tailoring guidance accordingly. Some may not exercise with BFR without risk. Interventions with lower risk must be encouraged when BFRT is deemed unsafe, or the risk outweighs potential benefits.

These recommendations herein aim to minimize the risk of adverse events in high-risk patients with comorbidities or other conditions that may decrease the safety profile of BFRT. However, it is essential to recognize that most exercising populations engage in leisure time physical activity with minimal negative acute or long-term outcomes. Unlike leisure time physical activity, BFRT likely needs some degree of supervision to minimize risk. Supervision by knowledgeable clinicians should theoretically reduce the occurrence of adverse events (e.g., numbness, nausea, hypertension, headache, venous thrombus, deterioration of ischemic heart disease, fainting, tingling, excessive pain, central retinal vein occlusion, and rhabdomyolysis) (Nakajima et al., 2006; Ozawa et al., 2015; Yasuda et al., 2017; Patterson and Brandner, 2018; de Queiros et al., 2021) especially when performed under those who adequately screen out high risk patients and use recommended guidelines (Patterson et al., 2019; Rolnick and Schoenfeld, 2020a,b; Rolnick et al., 2021) to structure exercise programming.

The clinician should contemplate some specific questions before the application of BFRT:

- Is my patient like the participants in the studies with BFRT?
- Does BFRT have a clinically relevant benefit (e.g., improved function or hypertrophy) that outweighs the potential risks of application?
- Is another treatment or method available that could provide similar results with less risk than BFRT?

For the risk assessment tool, previous recommendations and guidelines in chronic disease were adapted (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020; Pelliccia et al., 2021). Also, exclusion criteria from small clinical studies with BFRT were integrated. Something important to address is that BFRT practitioners (e.g., physiotherapy, physical education teacher, or strength and conditioning coaches) are required to have a necessary physiological and pathoanatomical background knowledge on these conditions to apply the proposed risk stratification. Due to the judgment required and lack of any formal credentialing processes for those engaging in disseminating BFRT knowledge to clinicians and other providers, physician consultation may be necessary to clarify complex medical problems or their severity (Rolnick et al., 2021).

THROMBOSIS RISK AND BLOOD FLOW RESTRICTION TRAINING

A recent systematic review concluded that exercise with BFR does not exacerbate the activation of coagulation or enhance fibrinolytic activity (Nascimento et al., 2019). However, the current body of literature with respect to risk of thrombosis resulting from BFRT does not completely exclude the potential for deep vein thrombosis (DVT) formation. A recent study evaluated the feasibility of BFRT (>125% of arterial occlusion pressure, AOP) in patients with incomplete spinal cord injury and increased risk for DVT (Stavres et al., 2018). After 4 days of the experimental protocol, participants had blood drawn for D-dimer analysis. The D-dimer cut off values are normally < 500 ng/mL and medically ill subjects whose D-dimer is elevated beyond this value constitute a subgroup with high risk of first DVT occurrence, DVT recurrence, and mortality in which prospective evaluation is necessary (Halaby et al., 2015). Participants who displayed an abnormally high quantitative D-dimer (>500 ng/mL) underwent a second bilateral leg ultrasound. Two showed an elevated D-dimer (>500 ng/mL) after 4 days of the experimental session, but no DVT was observed (Stavres et al., 2018). Of note, this study utilized pressures not recommended in clinical practice (125% AOP) (Patterson et al., 2019).

It is important to mention a case report of Paget-Schroetter Syndrome (PSS) after an acute BFRT session (Noto et al., 2017). PSS is an idiopathic subclavian vein thrombosis due to compression at the thoracic outlet. Prior to DVT formation, the individual reported suffering from localized edema on the left collarbone with mild tenderness for 6 years. When performing BFRT (30 min to 1 h, three times a week) she became aware of additional swelling, pain and discoloration of her left upper limb. Blood tests revealed a slight increase in her D-dimer (1.7 μg/mL) level and subsequently was diagnosed with PSS derived from thoracic outlet syndrome. Physicians suspect that stagnation of the blood flow due to pressure applied during BFRT, venous retraction and endothelial dysfunction of the left subclavian vein had likely caused the PSS. Also, another case study reported an adverse effect of BFRT on a patient with diabetic retinopathy and a central retinal vein occlusion that was preceded by a session of BFRT (Ozawa et al., 2015).

Nonetheless, there appears to be the potential for DVT formation in those that may have medically complex histories. Thus, concerns with the use of BFRT in medically compromised individuals is relevant (**Table 1**). In addition, a limited number of studies have measured other hemostatic markers to determine safety issues for DVT necessitating additional pre-screening to theoretically enhance safety (Nascimento et al., 2019). Markers such as antithrombin deficiencies, protein C, cofactor protein S, and homocysteine may help further stratify potential risk for

TABLE 1 | Summarizes concerns about the use of BFRT associated with DVT development in medically compromised populations.

Medical condition	Concerns about use of BFRT and DVT
Hypertension	• Patients with hypertension are in a hypercoagulative and potentially prothrombotic state. This increased thrombotic risk has primarily attributed to the endothelial dysfunction associated with hypertension. • Additionally, hypertension frequently presents with elevations in hemostatic factors such as P-selectin (platelet aggregator), fibrinogen, and PAI-1 (Yang et al., 2010).
Post-COVID-19 infection	• Patients with COVID-19 may develop both venous and arterial system coagulopathy caused by endotheliitis, hypercoagulopathy, and stasis (Sarkar et al., 2021).
Pregnancy/Postpartum women	• Pregnancy has been shown to result in elevations in fibrinogen, factor VII, factor VIII, von Willebrand factor, factor IX, factor X, factor XII, and PAI-1 which increases the risk of DVT formation (Prisco et al., 2005). • Other factors such as delivery method (cesarean section) and obesity, multiparity, and medical comorbidities increases the risk for DVT as well (Alsheef et al., 2020). • Following pregnancy, DVT risk is 5 times higher, and acquisition of a pulmonary embolism is 15 times more likely than during pregnancy (Heit et al., 2005). • Increases in pro-coagulant and decreases in anti-coagulants are observed in OCP users compared to non-users (Gunaratne et al., 2021).
Diabetes mellitus	• Patients with DM type 1 or type 2 are at increased risk of DVT due to systemic changes and endothelial dysfunction (Diabetes, 2019). • Hyperglycemia triggers vascular damage by an imbalance between nitric oxide (NO) and reactive oxidative species (ROS), platelet aggregation, inflammation, and increased expression of coagulant tissue factors like PAI-1 (Paneni et al., 2013; Kaur et al., 2018).
Rheumatoid arthritis and Chronic kidney disease	• Rheumatoid arthritis patients are at an elevated risk of VTEs, pulmonary embolisms and DVT formation compared to the general population (Li et al., 2021). • Elevated thrombogenic factors can help explain the excessive risk for CVD, and all appear in a greater proportion of CKD patients than the general populace (Levey et al., 1998).
Post-surgery	• The risk of DVT is increased 100-fold in the first 6 weeks following surgery (Bond et al., 2019) and pulmonary embolism risk is more significant in the 12 weeks following surgery in middle-aged women, which of course, will depend on the type of surgery (Sweetland et al., 2009). • The relative risk for thrombosis after hip and knee arthroplasty is 220 times higher in the first 6 weeks after surgery, 91.6 times higher after cancer surgery, and 87 times higher after vascular surgery highlighting that surgery of any kind increases risk of DVT formation (Sweetland et al., 2009).
Anabolic steroid users and certain ergogenic aids*	• Users have a high risk of suffering from thrombotic complications, cardiomyopathy, stroke, pulmonary embolism, fatal and non-fatal arrythmias, and myocardial infarction (Sculthorpe et al., 2012). • Anabolic steroid users have side effects such as dyslipidemia, polycythemia, hyperhomocystemia, hypercoagulability state, cardiac and vascular hypertrophy, impaired angiogenesis, redox imbalance, and cardiomyocyte apoptosis (Seara et al., 2020).

*BFRT, blood flow restriction training; DVT, deep vein thrombosis; VTE, venous thromboembolism; CVD, cardiovascular disease; OCP, oral contraception; PAI-1, plasminogen activator inhibitor-1; CKD, chronic kidney disease. *Anabolic/ergogenic agents are not considered a medically compromised population but exhibit heightened risk for negative vascular sequalae that predispose to DVTs.*

BFRT in those with comorbidities (Motykie et al., 2000; Caprini et al., 2004).

The following sections will introduce relevant background information and pre-screening processes regarding patients with diabetes mellitus, cardiovascular disease and hypertension, rheumatoid arthritis, chronic kidney disease, COVID-19 infection and those post-surgery as well as those patients who engage in the use of anabolic steroids, ergogenic substances, are pregnant/postpartum and those who are apparently otherwise healthy.

THROMBOSIS RISK ASSESSMENT BEFORE BLOOD FLOW RESTRICTION TRAINING

Considering the above-mentioned presentations that likely may be at an elevated risk of DVT formation secondary to a prothrombotic state, risk stratification for DVT is strongly encouraged to be included during the initial screening process prior to BFRT (Prisco et al., 2005; Yang et al., 2010; Paneni et al., 2013; Kaur et al., 2018; Gupta et al., 2020; Seara et al., 2020). The adapted thrombosis risk factor assessment from Caprini (Motykie et al., 2000; Caprini, 2005; Golemi et al., 2019) represents a useful tool and was previously used in BFRT studies as exclusion criteria (Loenneke et al., 2013, 2015; Jessee et al., 2018; **Table 2**). It may be possible that the Caprini risk assessment model is too stringent, and for a patient with a risk factor score of five (e.g., hip fracture), BFRT might still be a preferrable method for rehabilitation given medical clearance and a reasonable amount of recovery time has passed (Motykie et al., 2000; Caprini, 2005; Golemi et al., 2019). Nonetheless, the use of the International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) (Spyropoulos et al., 2011; Mahan et al., 2014; Rosenberg et al., 2014; Raskob et al., 2016) that incorporates seven well established and easy-to-implement clinical risk factors for DVT could be used when clinicians consider the Caprini risk assessment model (Motykie et al., 2000; Caprini, 2005; Golemi et al., 2019) not applicable for anamnesis.

TABLE 2 | Thrombosis risk factor assessment.

Patient's Name:_____
Age:_____
Sex:_____

Each risk factor represents 1 point	**Each risk factor represents 2 points**
☐ Abnormal pulmonary function (COPD); ☐ Acute myocardial infarction; ☐ Age between 41 and 59 years; ☐ Blood transfusions; ☐ Chemotherapy; ☐ Congestive heart failure (<1 month); ☐ Diabetes requiring insulin; ☐ History of inflammatory bowel disease; ☐ History of prior major surgery (<1 month); ☐ Length of a surgery > 2 h; ☐ Medical patient currently on bed rest; ☐ Minor surgery planned; ☐ BMI > 25–39; ☐ Obstructive pulmonary disease; ☐ Sepsis (<1 month); ☐ Serious lung disease including pneumonia (<1 month); ☐ Smoking; ☐ Swollen legs (current); ☐ Varicose veins; ☐ Other risk factors: easy bruising, for example, must be included as may represent a platelet disorder (Ballas and Kraut, 2008);	☐ Age 60–74 years; ☐ Arthroscopic surgery; ☐ BMI > 40; ☐ Central venous access; ☐ Immobilized plaster cast (<1 month); ☐ Laparoscopy surgery (>45 min); ☐ Major surgery (>45 min); ☐ Malignancy (present or previous); ☐ Patient confined to bed (>72 h);

Each risk factor represents 3 points	**Each risk factor represents 5 points**
☐ Age over 75 years; ☐ Any acquired congenital thrombophilia; ☐ Elevated anticardiolipin antibodies; ☐ Elevated serum homocysteine; ☐ Family history of thrombosis; ☐ Heparin-induced thrombocytopenia; ☐ History of DVT/PE; ☐ Positive Factor V Leiden; ☐ Positive lupus anticoagulant; ☐ Positive Prothrombin 20210A; ☐ If the answer is yes: ☐ Type:_____	☐ Acute spinal cord injury (paralysis) (<1 month); ☐ Elective major lower extremity arthroplasty; ☐ Hip, pelvis or leg fracture (<1 month); ☐ Multiple trauma (<1 month); ☐ Stroke (<1 month);

For women only (each represents 1 point)	**Total risk factor score**		
☐ History of unexplained stillborn infant, recurrent spontaneous abortion (≥3), premature birth with toxemia, or growth-restricted infant; ☐ Oral contraceptives or hormone replacement therapy; ☐ Pregnancy or postpartum (<1 month);	**Score**	**Incidence of DVT**	**Risk level**
	0–1	<10%	Low
	2	10–20%	Moderate
	3–4	20–40%	High
	5 or more	40–80% and risk of mortality of 1–5%	Highest

Adapted from Caprini (2005). DVT, deep vein thrombosis; PE, pulmonary embolism; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Using the IMPROVE risk assessment model, patients are classified into low-risk tier (0–1 points), moderate-risk tier (2–3 points), and high-risk tier (≥4 points) (**Table 3**; Spyropoulos et al., 2011; Mahan et al., 2014; Rosenberg et al., 2014; Raskob et al., 2016).

For individuals who are hypertensive, post-COVID-19 infection, post-surgery, have rheumatoid arthritis, chronic kidney disease, cardiovascular disease, diabetes mellitus or engage in anabolic agents/steroids and/or ergogenic substances, we recommend the use of Caprini or IMPROVE scales (Caprini, 2005; Rosenberg et al., 2014) for thrombosis risk assessment in addition to normal pre-screening processes.

Of note, use of BFRT during or closely following pregnancy/post-partum period is a contentious topic with

TABLE 3 | Modified IMPROVE risk score.

Patient's Name:_____
Age:_____
Sex:_____

DVT risk assessment	DVT risk score
Previous VTE	3
Known thrombophilia[a]	2
Current lower leg paralysis or paresis[b]	2
Prior cancer[c]	2
ICU/CCU stay	1
Complete immobilization ≥ 1 day[d]	1
Age ≥ 60 years	1

ICU, intensive care unit; CCU, cardiac care unit; VTE, venous thromboembolism. [a]A congenital or acquired condition leading to excess risk of thrombosis (e.g., factor V Leiden, lupus anticoagulant, factor C or factor S deficiency). [b]Leg falls to bed by 5 s, but has some effort against gravity or presence hemiparesis, hemiplegia, paraplegia, and quadriplegia. [c]Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet eligibility criteria). [d]Confined to bed or chair with or without bathroom privileges. Adapted from previous studies (Spyropoulos et al., 2011; Mahan et al., 2014; Rosenberg et al., 2014; Raskob et al., 2016).

regards to safety and potential DVT risk. Only one case study has been reported during pregnancy. The case report applied BFRT in the third trimester (1 set of 30 repetitions followed by 20 repetitions and then 15 repetitions, a rest interval of 20 s between sets, and with a setting pressure between 40 and 200 mmHg) using biceps curl with a 1 kg load with no negative influence on the fetal status and uteral-placental circulation (Takano et al., 2013). Despite the observations of no effect of BFRT on the female and the fetus, health professionals should exhibit caution when screening a female pregnant/postpartum prior to BFRT for thrombosis risk (Motykie et al., 2000; Caprini et al., 2004; Caprini, 2005). Considering that BFRT diminishes venous return, it is vital to understand the pathogenesis of DVT in pregnancy. Pregnant women have a 50% reduction in venous leg flow that begins to normalize by 6 weeks post-partum (Macklon and Greer, 1997; Brown and Hiett, 2010). Uteral growth impedes inferior vena cava and iliac vein flow, producing obstruction, increases in venous capacitance and blood stasis; all of which contribute to an elevated DVT risk (Brown and Hiett, 2010). As women usually become prothrombotic in pregnancy and the risk of DVT is higher, Caprini or IMPROVE scales (Caprini, 2005; Rosenberg et al., 2014) should not be used for this population.

Clinicians should consistently evaluate the pregnant patient for signs of venous thromboembolism (VTE) such as swelling and shortness of breath, changes in skin temperature, presence of tachycardia, pain or discoloration, and swollen or distended varicose veins in the affected limb (O'Brien et al., 2018). A simple clinical tool that has been used practically by the authors in other at-risk populations is taking periodic photographs of the affected limb every ∼4 weeks. If varicosities are increasing, it is strongly advised to discontinue BFRT.

Last, clinicians should be aware of May-Thurner syndrome (estimated prevalence of at least 20% in the general populace) during screening (Peters et al., 2012). May-Thurner syndrome occurs when the right iliac artery compresses the left iliac vein, predisposing the patient to iliac vein thrombosis and painless unilateral leg swelling (Golemi et al., 2019).

DIABETES MELLITUS AND BLOOD FLOW RESTRICTION TRAINING

A recent review study cited possible theoretical positive benefits of BFRT in patients in both type 1 (Jones et al., 2021) and type 2 diabetes mellitus (DM) (Saatmann et al., 2021). Satoh (2011) showed beneficial effects of BFRT on 51 cases with metabolic syndrome, as evidenced in a 10% drop in systolic blood pressure (SBP) and diastolic blood pressure (DBP), a 10% drop in HbA1c levels, an 8% decrease in LDL cholesterol and a 10% weight loss with no adverse events reported. Unfortunately, the study did not include a control group, limiting the ability to extrapolate whether the observed effects were from the exercise, the BFRT, or both. Nonetheless, the results support the use of BFRT in this population with clinically relevant improvements in hemodynamics and relevant metabolic syndrome markers. In addition, a recent study on rats with DM displayed that BFRT plus electrical stimulation prevented diabetes-associated muscle atrophy, highlighting that muscular responses to BFR exercise can be elicited despite the impaired systemic changes (albeit with evoked electrical stimulation) (Tanaka et al., 2019).

Recently, only one experimental study displayed that low-intensity BFRT resistance exercise compared to high-intensity resistance exercise in females with DM type 2 induces thrombocytosis (excessive number of platelet count and plateletcrit) but with similar platelet activation markers to high-intensity resistance training (Fini et al., 2021). This acute response might demonstrate the safety and potential useful of BFRT in this population compared to traditionally recommended approaches to strength training.

However, considering the low level of evidence in this particular population, we have only one study with DM patients (Fini et al., 2021). In the presence of any of the following risk factors cited below (**Table 4**), the patient with DM is classified as high risk (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020), precluding the use of BFRT without physician clearance.

TABLE 4 | Relevant risk factors concerning DM patients before beginning BFRT.

Patient's Name:_____
Age:_____
Sex:_____

☐ *Patients with diabetes mellitus without organ damage with DM duration ≥ 10 years or another additional risk factor[a];
☐ *Type 1 diabetes mellitus of long duration (>20 years);
☐ *Premature family history of cardiovascular disease[b];
☐ *Presence of metabolic syndrome (Alberti et al., 2009)[c];
☐ *Untreated systemic arterial hypertension;
☐ *Current smoker[d];
☐ *Diabetes mellitus with target organ damage[e];
☐ *Cardiovascular autonomic neuropathy;
☐ *Diabetic retinopathy;
☐ *Glycemia > 250 mg/dL with or without ketosis prior exercise;
☐ *Coronary calcium score > 10 Agatstone;
☐ *Carotid plaque (intima-media thickness > 1.5 mm);
☐ *Angiotomography of the coronary arteries with the presence of plaque;
☐ *Ankle-brachial index < 0.9;
☐ *Presence of abdominal aortic aneurysm;
☐ *Acute coronary syndrome;
☐ *Ischemic stroke or transient ischemic attack;
☐ *Peripheral vascular insufficiency (ischemic ulcer);
☐ *Revascularization of any artery for atherosclerosis: carotid, coronary, renal, and lower limbs;
☐ *Non-traumatic amputation of lower limbs;
☐ *Severe atherosclerotic disease with obstruction > 50% in any artery;
☐ Acute systemic illness;
☐ Angina or ischemic ST depression at a workload < 6 METs;
☐ Cardiomyopathy with ejection fraction < 30%;
☐ Complex ventricular arrhythmias not well controlled;
☐ Congenital heart disease;
☐ Coronary revascularization (percutaneous coronary interventions, coronary by-pass graft surgery, and other arterial revascularization procedure);
☐ Exercise capacity < 6 METs;
☐ Fall in systolic blood pressure below resting levels during exercise;
☐ Familial hypercholesterolemia with atherosclerotic cardiovascular disease or with another major risk factor;
☐ Marked elevated single risk factors, in particular total cholesterol (>310 mg/dL), LDL-C (>190 mg/dL), or blood pressure ≥ 180/110 mmHg;
☐ Multivessel coronary disease with two major epicardial arteries having 50% of stenosis;
☐ Myocardial infarction and unstable angina;
☐ Non-sustained ventricular tachycardia with exercise;
☐ Peripheral artery disease;
☐ Previous episode of primary cardiac arrest (e.g., cardiac arrest that did not occur in the presence of an acute myocardial infarction or during a cardiac procedure);
☐ Self-reported easy bruising (Ballas and Kraut, 2008);
☐ Stable angina;
☐ Stroke;
☐ Transient ischemic attack;
☐ Valvular heart disease with severe and asymptomatic valvular stenosis or regurgitation;
☐ SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg prior to exercise;
☐ Other medical condition that could be aggravated by exercise;
☐ A medical problem that the physician and BFRT-user believe may be life-threatening;

*[a]Valid for individuals with ≥ 18 years. [b]Presence of cardiovascular disease in a first-degree relative (only father, mother, or siblings) before aged 55 (men) and under 65 (women). [c]Waist circumference ≥ 94 cm for men and ≥ 102 cm for women; elevated triglycerides (≥150 mg/dL) or drug treatment for elevated triglycerides; HDL-C < 40 mg/dL in males and < 50 in females or drug treatment for reduced HDL-C; SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg or drug treatment for elevated blood pressure; fasting glucose ≥ 100 mg/dL or drug treatment for elevated glucose. [d]At least 1 year without smoking or similar. HDL, high density lipoprotein. [e]Retinopathy, neuropathy, left ventricular hypertrophy; Carotid artery intima-media thickness > 0.9 mm or carotid plaque; Carotid-femoral pulse wave velocity > 10 m/s; Ankle-brachial index < 0.9; Stage 3 chronic kidney disease; Albuminuria between 30 and 300 mg/24 h or albumin-creatinine ratio urinary 30–300 mg/g. SBP, systolic blood pressure; DBP, diastolic blood pressure. *, risks are specific for diabetic patients. Adapted from previous studies (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020; Pelliccia et al., 2021).*

Diabetes mellitus patients display elevated levels of plasma homocysteine, soluble endothelial protein receptor (sEPCR) and high sensitivity C reactive proteins (hsCRP) signaling a pro-inflammatory state (van Guldener and Stehouwer, 2002; Zaghloul et al., 2014). Hyperglycemia on endothelial cells closely mimics that of inflammatory initiators (Funk et al., 2012). Furthermore, in DM type 1, sEPCR is associated with duration of the disease and hsCRP is associated with duration of disease and hypertension (Zaghloul et al., 2014). These changes have marked effects on fibrin structure-function, generating a denser clot with greater resistance to fibrinolysis (Grant, 2007). Factors such as decreased NO availability, oxidative stress

(ROS imbalances), smooth muscle cell proliferation, increased leukocyte adhesion, enhanced platelet aggregation, and impaired fibrinolysis also increase DVT risk (van Guldener and Stehouwer, 2002; Zaghloul et al., 2014). Furthermore, considering that DM may remain undetected for many years and its diagnosis is often made incidentally, clinicians may encounter this disease at an advanced stage when vascular complications have already occurred (Beckman et al., 2013).

As DM is associated with a prothrombotic state (Paneni et al., 2013; Kaur et al., 2018), risk stratification for DVT (**Tables 2**, **3**) in conjunction with the previous risk factors must be included (**Table 4**). However, clinicians should use clinical judgment, knowledge of risk factors, and experience to provide protection to the patient along with consulting other clinician experts/physicians when unsure of risk (Rolnick et al., 2021).

If the clinician decides to proceed with BFRT, frequent blood pressure monitoring during exercise sessions (e.g., during the exercise bout or during the rest periods between sets) is strongly recommended until safety is established (2–4 weeks) for those at moderate-to-high risk of cardiac complications during exercise (Fletcher et al., 2001). Further, when exercise positions are changed (e.g., seated leg extensions to standing squats), monitoring of blood pressure responses should be performed as the hemodynamic responses to exercise will likely differ (Hughes et al., 2018). Similarly, clinicians working with a patient with DM may also apply routine diabetic screening precautions. These include insulin checks, possibly evaluating ketone levels, verifying recent episodes of hypoglycemia, carbohydrate intake before and after exercise and monitoring for post-exercise hypoglycemia depending on professional scope of practice (Milech et al., 2016; Adolfsson et al., 2018; Diabetes, 2019).

HYPERTENSION, BLOOD PRESSURE, HEART RATE VARIABILITY, ANGIOGENESIS AND BLOOD FLOW RESTRICTION TRAINING

Concerns about BFRT were raised previously on the effect of exercise with BFR when compared to exercise without BFR on hemodynamic and endothelial function. Shear stress is an important factor for inducing endothelial adaptation during exercise and is a major stimulus for NO release from the endothelium (Phillips et al., 2015). However, acute application of BFRT has exhibited lower shear stress and higher retrograde shear stress post-BFRT, suggesting a blunted reactive hyperemic response (da Cunha Nascimento et al., 2020b). Another study reported no changes in endothelial function or worsening changes when compared to the non-cuffed arm, highlighting the potential for attenuated local vascular adaptations with chronic BFRT exercise protocols (Tinken et al., 2010).

Some studies report acute reductions in flow-mediated dilation (FMD) (an essential index of endothelial function) for upper limbs (radial artery) and lower limbs (popliteal artery) with long-term reduction of FMD for upper limbs when compared to exercise without BFR (Credeur et al., 2010; Renzi et al., 2010; Tinken et al., 2010; Paiva et al., 2016). Thus, low shear stress and increased retrograde shear stress promoted by cuff use may contribute to endothelial dysfunction (Thijssen et al., 2009). Further support for potential endothelial dysregulation came from a previous study who reported increased DBP and mean arterial pressure response after a chronic low load BFRT protocol (Kacin and Strazar, 2011). These results may be of particular concern to individuals with hypertension as they show significantly greater SBP and DBP response compared to normotensive subjects during BFRT (Domingos and Polito, 2018).

A recent meta-analysis demonstrated that regular BFRT exercise elicits a significant 4.2 mmHg SBP increase over time (Wong et al., 2021). While small, those results may evoke safety concerns in those populations whose exercise pressor reflex may be altered such as in those with hypertension, heart failure, and peripheral arterial disease (Spranger et al., 2015; Cristina-Oliveira et al., 2020). However the findings from that meta-analysis were limited to a low number of included studies (4 studies) and a lack of a sub-group analysis taking into consideration absolute occlusion pressure, cuff width and occlusion pressure prescription (e.g., personalized vs. arbitrary values) on hemodynamic outcomes. Furthermore, a previous systematic review and meta-analysis demonstrated that values of SBP and DBP were significantly higher for hypertensive individuals compared to normotensive individuals during BFRT (Domingos and Polito, 2018). Nonetheless, as BFRT generates exaggerated increases in the sympathetic nervous system activity relative to work matched free flow exercise, this may precipitate adverse cardiovascular or cerebrovascular events, as BFR adds ∼5–10 mmHg to the usual blood pressure response during resistance training (Spranger et al., 2015; Cristina-Oliveira et al., 2020).

Other parts of the vascular system are similarly stressed during BFRT. A previous study demonstrated that BFRT in healthy subjects could acutely increase venous hypertension by ∼60 mmHg (Franz et al., 2020). While a healthy venous system can likely tolerate these increases with functioning venous valves in a longitudinal training program, patients with venous insufficiency or postoperative lymphedema might experience worsening of the cardiovascular health status induced by BFRT (Franz et al., 2020).

Results in the literature are mixed regarding exaggerated pressor responses, arterial blood pressure responses and autonomic modulation. With respect to the exercise pressor reflex, some studies evaluated the acute and chronic effects of BFRT and heart-rate variability and hemodynamic responses. The acute responses displayed in healthy older adults demonstrated that high intensity aerobic exercise (70% of VO_2max) increased sympathetic-vagal balance and delayed vagal modulation at post-30 min recovery when compared to low load BFRT (using 50% AOP) (Ferreira et al., 2017). Also, a study using BFRT following an acute bout of bench-press exercise displayed decreased vagal modulation post-30 min for both low load BFRT (using rating of tightness at "7 of 10") and high load but with a significant reduction after high load compared to low load (Tai et al., 2019). Furthermore, a previous study demonstrated

that BFRT with 60% AOP compared to 80% AOP resulted in a reduction of SBP and DBP and increased vagal modulation after 48 h of an acute exercise session in older women with metabolic syndrome (Maciel et al., 2020). Conversely, BFRT with 80% AOP increased SBP by 15 mmHg immediately after the exercise session, possibly associated with higher metabolic stress during exercise and greater stimulation of the exercise pressor reflex. More research is needed to link BFRT application parameters along with responses to various loads with magnitude of exercise pressor responses in healthy and at-risk populations.

Regarding autonomic modulation and recovery, a previous study showed that heart rate variability (HRV) was delayed and accompanied by a significant reduction over time after single unilateral high intensity leg press exercise session compared to BFRT (Okuno et al., 2014). These results suggest a greater blunted parasympathetic recovery compared to BFRT (using an arbitrary pressure of 100 mmHg). The elevated lactate levels observed during high intensity exercise displayed a negative correlation with HRV, suggesting a blunted parasympathetic recovery [e.g., the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) and high frequency (HF) indices] compared to BFRT. The chronic effects of BFRT compared to traditional high load resistance training on HRV in inactive older adults (some of them with DM, hypertension, dyslipidemia, and venous insufficiency) demonstrated that after 12 weeks of resistance training, no training-related changes between groups were observed in HRV (Lopes et al., 2021). Nevertheless, only BFRT induced decrements of approximately seven mmHg for SBP and five mmHg for DBP. Hence, blood pressure reduction in the BFRT group may have resulted from vascular mechanisms such as angiogenesis and improved endothelial function despite potential acute increases in hemodynamic responses during exercise.

The effect of BFRT on angiogenesis or relevant transcription factors has been shown in both acute and longitudinal studies. Following an acute bout of exercise, BFRT increased vascular endothelial growth factor (VEGF), hypoxia-inducible factor 1 alpha (HIF-1α), isoforms nitric oxide synthase (eNOS), and VEGF receptors as kinase insert domain receptor (KDR) (Larkin et al., 2012; Ferguson et al., 2018). In addition, the acute effects of BFRT increase angiotensin-converting enzyme 2 (ACE2) and bone marrow-derived CD34 + hematopoietic stem/progenitor cells, markers associated with positive vascular and muscle health (Joshi et al., 2020). Furthermore, angiogenic adaptations following 3 weeks of BFRT have been shown to increase capillary number per myofiber and capillary area (Nielsen et al., 2020). Another study displayed increased reactive hyperemia index and transcutaneous oxygen pressure in the foot after 4 weeks of BFRT, indicating improved peripheral blood circulation compared to non-BFRT in healthy older adults (Shimizu et al., 2016).

However, positive effects on angiogenesis may ultimately depend on balancing training volume and frequency. A previous study demonstrated an adverse effect of low load resistance training with BFR (using a protocol of multiple sessions of BFRT per day) (Nielsen et al., 2020). A few participants displayed a transient thickening of the perivascular basal membrane while five participants showed basal lamina thickening 10 days after cessation of the intervention. Thickening of the perivascular basal membrane is associated with diseases like hypertension, peripheral artery disease, DM, inflammation, and miscellaneous disorders (Baum and Bigler, 2016). Triggers include high hemodynamic forces, congestion of venous blood flow and chronic hypoxia (Baum and Bigler, 2016). Degeneration of pericytes accompanying thickening of the basal lamina increases the distance of oxygen and nutritional substrates required to reach muscle fibers and may impair contractile activity during exercise caused by the limited energy supply (Baum and Bigler, 2016). Another study demonstrated that 4 non-failure sets of low load knee extension exercise with BFR (at 60% AOP) mitigated the increase of circulating endothelial progenitor cells (CD34 + VEGFR2 + and CD34 + CD45dimVEGFR2 +) in healthy male adults (Montgomery et al., 2019). In contrast, exercise without BFR resulted in a statistically significant increase in circulating endothelial progenitor cells (Montgomery et al., 2019). Although speculative, there may be an influence on the cellular responses observed that is dependent on individual characteristics, the BFRT protocol used and/or the timing of the blood draws.

Considering the information presented, in the presence of any of the following risk factors cited in **Table 5**, the patient with hypertension is classified as high risk (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020), precluding the use of BFRT without physician clearance.

CARDIOVASCULAR DISEASE AND BLOOD FLOW RESTRICTION TRAINING

Few studies have reported the effect of BFRT on patients with cardiovascular disease. Thus far, only 4 pilot studies (1 acute, 3 longitudinal) have been performed. The first study evaluated the post-exercise hemostatic and inflammatory responses of a BFRT session in 9 patients with stable ischemic heart disease (Madarame et al., 2013). The protocol consisted of four sets of knee extension exercise at an intensity of 20% 1RM (30-15-15-15 repetitions) using an arbitrary applied pressure of 200 mmHg. Sympathetic responses were heightened in the BFRT condition as evidenced by a significant increase in mean difference of noradrenaline (1.04 nmol/L^{-1}) over the non-BFRT group. Irrespective of group allocation, post-exercise mean levels of D-dimer (0.07 μg/mL^{-1}) and serum CRP increased compared to pre-exercise (51.3 ng/mL^{-1}) baseline values, indicating a lack of an effect of BFRT on these hemostatic and inflammatory markers. However, D-dimer levels remained within a clinically normal range (<500 ng/mL) (Halaby et al., 2015), supporting the acute safety profile of BFRT in this small sample of patients.

The second pilot study evaluated the effects of 3 months of BFRT in 21 patients who underwent cardiovascular surgery (Ogawa et al., 2021). Patients were randomly assigned to a standard cardiac rehabilitation program (30 min of aerobic exercise twice a week for 3 months within the anaerobic threshold on a cycle ergometer) and resistance training with BFR (n = 11) or without BFR (n = 10) on leg extension and leg press starting

TABLE 5 | Relevant risk factors concerning cardiovascular and hypertensive clients/patients before BFRT.

Patient's Name:_____
Age:_____
Sex:_____

☐ Acute myocarditis;
☐ Acute systemic illness;
☐ Angina or ischemic ST depression at a workload < 6 METs;
☐ Angiotomography of the coronary arteries with the presence of plaque;
☐ Aortic syndrome or venous thromboembolism;
☐ Cardiomyopathy with ejection fraction < 30%;
☐ Class III or IV heart failure;
☐ Complex ventricular arrhythmias not well controlled;
☐ Congenital heart disease;
☐ Coronary revascularization (percutaneous coronary interventions, coronary by-pass graft surgery, and other arterial revascularization procedure);
☐ Electrocardiographic alterations at rest or during effort;
☐ Endocarditis, or pericarditis;
☐ Exercise capacity < 6 METs;
☐ Fall in systolic blood pressure below resting levels during exercise;
☐ Familial hypercholesterolemia with atherosclerotic cardiovascular disease or with another major risk;
☐ Marked elevated single risk factors, in particular total cholesterol (>310 mg/dL), LDL-C (>190 mg/dL), or blood pressure ≥ 180/110 mmHg;
☐ Multivessel coronary disease with two major epicardial arteries having 50% of stenosis;
☐ Myocardial infarction and unstable angina;
☐ Non-sustained ventricular tachycardia with exercise;
☐ Peripheral artery disease;
☐ Postural hypotension (20 mmHg drop in systolic blood pressure with symptoms of dizziness or light-headedness);
☐ Presence of abdominal aortic aneurysm;
☐ Previous episode of primary cardiac arrest (e.g., cardiac arrest that did not occur in the presence of an acute myocardial infarction or during a cardiac procedure);
☐ Recent myocardial infarction < 3 months;
☐ SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg prior to exercise;
☐ SBP between 130 and 139 mmHg or DBP between 85 and 89 mmHg with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ SBP between 140 and 159 mmHg or DBP between 90 and 99 mmHg with the presence of three or more cardiovascular risk factors[a], with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ SBP between 160 and 179 mmHg or DBP between 100 and 109 mmHg with the presence of 1 cardiovascular risk factor[a], with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ Self-reported easy bruising (Ballas and Kraut, 2008);
☐ Severe and/or symptomatic valve disease;
☐ Severe pulmonary hypertension;
☐ Stable angina;
☐ Stroke;
☐ Transient ischemic attack;
☐ Uncontrolled dysrhythmias;
☐ Unstable angina;
☐ Valvular heart disease with severe and asymptomatic valvular stenosis or regurgitation;
☐ Other medical condition that could be aggravated by exercise;
☐ A medical problem that the physician and BFR-user believe may be life-threatening;

[a]Men ≥ 55 years or women ≥ 65 years; History of premature CVD in 1st degree relatives: men < 55 years old or women < 65 years old; Smoking; Dyslipidemia: total cholesterol > 190 mg/dL and/or LDL-cholesterol > 115 mg/dL and/or HDL-cholesterol < 40 mg/dL in men or < 46 mg/dL in women and/or Triglycerides > 150 mg/dL; Insulin resistance: fasting plasma glucose between 100 and 125 mg/dL, oral glucose tolerance test between 140 and 199 mg/dL in 2 h, glycated hemoglobin between 5.7 and 6.4%; Obesity: BMI ≥ 30 kg/m^2, waist circumference ≥ 102 cm for men or ≥ 88 cm for women. [b]Left ventricular hypertrophy; Carotid artery intima-media thickness > 0.9 mm or carotid plaque; Carotid-femoral pulse wave velocity > 10 m/s; Ankle-brachial index < 0.9; Stage 3 chronic kidney disease; Albuminuria between 30 and 300 mg/24 h or albumin-creatinine ratio urinary 30–300 mg/g. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index. Adapted from previous studies (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020; Pelliccia et al., 2021).

at post-op day 5–7. Cuff pressure in the BFRT group was set at 100 mmHg and gradually increased to 160–200 mmHg over 2–3 weeks. During training, vital signs, electrocardiogram and rate of perceived exertion were continuously monitored. All patients received warfarin to reduce risk of post-surgical acquisition of a DVT with researchers closely controlling the prothrombin time-international normalized ratio. Markers of muscle damage (creatine phosphokinase), DVT markers (D-dimer) and adverse events were monitored in all patients. After 3 months, levels of muscle damage and D-dimer were within standard ranges and no adverse events were reported in the BFRT group, supporting its safety in the short-to-medium term post-surgery in cardiac rehabilitation patients. Paired with greater improvements in muscle mass [+20% (BFRT) vs. −4.3% (no BFRT)], muscle strength [+37% (BFRT) vs. + 9.1% (no BFRT)] and physical function [+26.4% (BFRT) vs. −5.4% (no BFRT)], this study supports the early integration of BFRT in this patient cohort (Ogawa et al., 2021).

The third pilot study evaluated the effects of 8 weeks of BFRT on leg extension strength (30% of 1RM with cuff inflated between

15 and 20 mmHg greater than brachial systolic pressure) along with hemodynamic, vascular function, and blood markers in patients with stable coronary artery disease (>3 months after acute coronary syndrome, revascularization, and/or documented by coronary angiography) (Kambic et al., 2019). Similar to literature on healthy individuals and other clinical populations (Hughes et al., 2017), BFRT increased muscle strength [+16.37% (BFRT) vs. + 5.29% (control group)] with reductions in SBP (−7 mmHg) and a tendency of better endothelial function ($p = 0.079$) (evaluated by FMD).

In addition, the same research group using the previous protocol evaluated the effect of 8 weeks of BFRT on hemodynamic and hemostatic markers in patients with stable coronary artery disease (>3 months after acute coronary syndrome, revascularization, and/or documented by coronary angiography). BFRT decreased SBP (−7 mmHg) compared to control group with no alterations on N-terminal prohormone B-type natriuretic hormone (212 ng/L), fibrinogen (2.94 g/L), and D-dimer levels (308 μg/L). Displaying no hazardous augmented hemodynamic response and beneficial effects on coagulation biomarkers, this study supports that use of BFRT can reduce cardiac stress through reductions in SBP without negatively altering clotting pathways (Kambic et al., 2021).

However, considering the aforementioned interventions were pilot studies, applying results to all ischemic and coronary artery diseases patients warrant caution. Particular concern should be given to acute sympathetic responses (noradrenaline) and the influence of a likely altered exercise pressor response in a potentially compromised cardiac system (Takano et al., 2005; Madarame et al., 2008; Shimizu et al., 2016). Thus, in the presence of any of the following risk factors cited above, the patient with concomitant hypertension and cardiovascular disease should likely avoid BFRT and another modality should be incorporated into the plan of care (Madarame et al., 2013; Malachias et al., 2016; Pinto et al., 2018; Kambic et al., 2019, 2021). We recognize this may be perceived as overly cautious, but clinicians are encouraged to actively collaborate with members of the medical team to ultimately determine BFRT candidacy if the patient may benefit from BFRT yet appears to have one or more risk factors present.

Risk stratification for DVT (**Tables 2**, **3**) in conjunction with the table below are strongly encouraged to be included in the decision-making risk assessment (**Table 5**). The clinician should use sound judgment, have knowledge of relevant risk factors, and draw on experience to reduce risk to the patient when integrating BFRT. Strategies to theoretically reduce risk to the patient are similar to those just beginning BFRT and have been discussed elsewhere (Rolnick et al., 2021).

RHEUMATOID ARTHRITIS AND BLOOD FLOW RESTRICTION TRAINING

BFRT has also been applied in autoimmune diseases like rheumatoid arthritis (RA). The first randomized controlled clinical trial evaluated the effects of BFRT (at 70% of AOP) after 12 weeks (twice a week) compared to high load RT in muscle strength, muscle mass, physical function, and quality of life. Similar increases in muscle strength [24.2% (high load RT) vs. 23.8% (BFRT)], muscle mass [10.5% (high load RT) vs. 9.5% (BFRT)] and physical function tests [14.7% (high load RT) vs. 11.2% (BFRT)] were observed. Only BFRT showed significant improvements in short form 36 health survey (SF-36) domains as physical and bodily pain and a significant reduction in visual analog scale (VAS) were reported (Rodrigues et al., 2020). For side effects, one patient withdrew from the study due to exercise-induced patellofemoral pain in the high load RT. Additionally, eight patients reported knee pain in the high load RT, requiring reductions of the load and repetitions (Rodrigues et al., 2020).

The second randomized controlled trial evaluated the effects of 4 weeks (three times a week, using 50% AOP) of low load BFRT compared to low load exercise training without BFRT on side effects, perceived pain, general satisfaction, and muscle strength. The interventions produced similar side effects in both groups. However, a case of headache and a cramping tendency in the calf muscles in one participant in the BFRT group was observed. For VAS, no changes for both groups from baseline and between groups were observed. Also, participants showed good compliance with training. For strength measurements, both groups improved muscle strength [23.2% (BFRT) vs. 17.8% (no BFRT)] (Jonsson et al., 2021).

Nevertheless, the literature reports that autoimmune disease-associated hypertension, premature atherosclerosis, myocardial dysfunction, electrical abnormalities, valvular involvement, pericarditis, and congestive heart failure lead to increased cardiovascular disease in RA patients (Faccini et al., 2016; Buleu et al., 2019; Wolf and Ryan, 2019). The prevalence of hypertension in RA patients appears to be slightly higher (Panoulas et al., 2008). Medications such as non-selective non-steroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase II inhibitors (coxibs), glucocorticoids (GC), and some modifying antirheumatic drugs (DMARDs) should be screened for before beginning BFRT as they may cause hypertension and interfere with its effective control (Panoulas et al., 2008).

Risk stratification for RA patients should include screening for DVT risk (**Tables 2**, **3**) as these patients are at an elevated risk of VTEs, pulmonary embolisms and DVT formation compared to the general population (Li et al., 2021). In conjunction with DVT screening, in the presence of any of the following risk factors cited below without physician clearance, the patient with RA should avoid BFRT, and another modality should be used (**Table 6**).

CHRONIC KIDNEY DISEASE AND BLOOD FLOW RESTRICTION TRAINING

BFRT may become a potentially valuable tool for chronic kidney disease (CKD) patients as they present low tolerance to heightened perceptual demands of exercise training (Correa et al., 2021a,b; de Deus et al., 2021; Deus et al., 2022). Randomized controlled trials using the same protocol compared the effects of 6 months of periodized resistance training with and without BFRT 3 days a week in male and female

TABLE 6 | Risk factors concerning rheumatoid arthritis patients before BFRT.

Patient's Name:_____
Age:_____
Sex:_____

☐ Unstable angina;
☐ Electrocardiographic alterations at rest or during effort;
☐ Recent myocardial infarction < 3 months;
☐ Class III or IV heart failure;
☐ Uncontrolled dysrhythmias;
☐ Severe pulmonary hypertension;
☐ Severe and/or symptomatic valve disease;
☐ Aortic valve stenosis;
☐ Aortic aneurism;
☐ Raynaud's phenomenon;
☐ Acute myocarditis;
☐ Endocarditis, or pericarditis;
☐ Aortic syndrome or venous thromboembolism;
☐ Acute systemic illness;
☐ Coronary calcium score > 10 Agatstone;
☐ Carotid plaque (intima-media thickness > 1.5 mm);
☐ Angiotomography of the coronary arteries with the presence of plaque;
☐ Presence of abdominal aortic aneurysm;
☐ Exercise capacity < 6 METs;
☐ Angina or ischemic ST depression at a workload < 6 METs;
☐ Fall in systolic blood pressure below resting levels during exercise;
☐ Non-sustained ventricular tachycardia with exercise;
☐ Previous episode of primary cardiac arrest (e.g., cardiac arrest that did not occur in the presence of an acute myocardial infarction or during a cardiac procedure);
☐ SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg prior to exercise;
☐ Uncontrolled hypertension (>180/110 mmHg);
☐ SBP between 160 and 179 mmHg or DBP between 100 and 109 mmHg with the presence of 1 cardiovascular risk factor[a], with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ SBP between 140 and 159 mmHg or DBP between 90 and 99 mmHg with the presence of three or more cardiovascular risk factors[a], with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ SBP between 130 and 139 mmHg or DBP between 85 and 89 mmHg with target organ damage[b], chronic kidney disease or diabetes mellitus;
☐ Postural hypotension (20 mmHg drop in systolic blood pressure with symptoms of dizziness or light-headedness);
☐ Marfan's syndrome;
☐ Prednisolone > 5 mg/day over the past 3 months;
☐ Self-reported easy bruising (Ballas and Kraut, 2008);
☐ Other medical condition that could be aggravated by exercise;
☐ A medical problem that the physician and BFR-user believes may be life-threatening;

[a]Men ≥ 55 years or women ≥ 65 years; History of premature CVD in 1st degree relatives: men < 55 years old or women < 65 years old; Smoking; Dyslipidemia: total cholesterol > 190 mg/dL and/or LDL-cholesterol > 115 mg/dL and/or HDL-cholesterol < 40 mg/dL in men or < 46 mg/dL in women and/or Triglycerides > 150 mg/dL; Insulin resistance: fasting plasma glucose between 100 and 125 mg/dL, oral glucose tolerance test between 140 and 199 mg/dL in 2 h, glycated hemoglobin between 5.7 and 6.4%; Obesity: BMI ≥ 30 kg/m^2, waist circumference ≥ 102 cm for men or ≥ 88 cm for women. [b]Left ventricular hypertrophy; Carotid artery intima-media thickness > 0.9 mm or carotid plaque; Carotid-femoral pulse wave velocity > 10 m/s; Ankle-brachial index < 0.9; Stage 3 chronic kidney disease; Albuminuria between 30 and 300 mg/24 h or albumin-creatinine ratio urinary 30–300 mg/g. SBP, systolic blood pressure; DBP, diastolic blood pressure; CVD, cardiovascular disease; LDL, low density lipoprotein; HDL, high density lipoprotein; BMI, body mass index. Adapted from previous studies (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020; Rodrigues et al., 2020; Jonsson et al., 2021; Pelliccia et al., 2021).

patients with stage 2 CKD with hypertension and DM. The training included eight exercises: bench press, seated row, shoulder press, triceps pulley, barbell curls, leg press 45°, leg extension, and leg curl. Fifty percent (50%) of AOP was applied for the upper and lower limbs in a continuous application method during all exercise training sessions. Chronic effects of resistance training in this population from BFRT compared to traditional training include increased angiotensin 1-7, NO2-, increased antioxidant defense, decreased pro-oxidative markers, increased catalase activity, improved glucose homeostasis and hormones mediators of glucose uptake, and improved cardiac autonomic function (Correa et al., 2021a,b; de Deus et al., 2021; Deus et al., 2022). At the same time, BFRT diminished vasopressin levels and attenuated the decrease of estimated glomerular filtration, implying positive post-exercise benefits. Also, improved uremic parameters and inflammation profile (e.g., interleukin-6, IL-10, IL-15, IL-17a, IL-18, klotho, C-reactive protein, and tumor necrosis factor-alpha) was observed in the BFRT group indicating downregulation of inflammation-related markers and a decreasing of fibroblast growth factor 23 (marker of renal deterioration)-klotho axis (Correa et al., 2021a,b; Deus et al., 2022).

Other studies using BFRT on CKD patients demonstrated health benefits in end stage CKD (Cardoso et al., 2020). One 12-week randomized clinical trial evaluated the effect of intradialytic exercise with BFR (cycle ergometry during hemodialysis sessions three times a week) compared to conventional exercise on walking endurance test. Fifty percent of AOP was applied to the lower limbs continuously during all training sessions. Results of this study demonstrated no differences in functional capacity (walking distance in 6 min) between groups despite a larger improvement in walked distance

in the BFRT group. BFR (at 50% of AOP) was applied during cycling exercise for 20 min within the first 2 h of hemodialysis with rate of perceived exertion of 12–13 (RPE Borg scale). Also, BFRT was shown effective as exercise alone in improving hemodialysis adequacy (e.g., how well blood is being cleansed), displaying a positive result in single-pool Kt/V-urea, equilibrated Kt/V-urea, urea reduction ratio, and urea rebound (Dias et al., 2020).

For adverse reports using BFR in CKD patients, a randomized clinical trial examined patients in three conditions using a cycle ergometer with bilateral BFR—non-BFR exercise during dialysis, BFR exercise off dialysis, and BFR exercise during dialysis (5 min of warm-up followed by two bouts of 10 min of cycling separated by 20 min of rest at 50% AOP). One case of exercise-related syncope (systolic and diastolic blood pressure of 88 and 68 mmHg, respectively) occurred with BFRT during hemodialysis. However, the participant chose to remain enrolled in the study. Also, in the same study, one additional instance of a participant feeling "light-headed" in recovery was reported. However, this was self-resolving, and ultrafiltration resumed within 5 minutes. Another randomized clinical study compared the effects of 8 weeks of exercise training including tennis ball, dumbbell weights, and handgrip exercise five times a week between BFRT group and exercise training alone observed isolated reports of tingling and fatigue in the upper limb of some patients who underwent BFRT at the time of exercise; however, these complaints were not sufficient for them to withdraw from the study (Silva et al., 2021).

Thus, BFRT may be a promising strategy for CKD patients to improve physical functioning and medical management of their condition. However, CKD patients are considered in the highest group for subsequent cardiovascular disease events (Levey et al., 1998). Traditional risk factors as advanced age, hypertension, hyperlipidemia, diabetes, and physical inactivity in conjunction with the patient characteristics of CKD (e.g., proteinuria, increased extracellular fluid (ECF) volume, electrolyte imbalance, anemia, and elevated thrombogenic factors) can help explain the excessive risk for CVD, and all appear in a greater proportion of CKD patients than the general populace (Levey et al., 1998). Besides, BFRT raises concerns as most stage III and IV CKD patients demonstrate hypertension and enhanced sensitivity of vascular α1-adrenergic receptors that may explain the more significant blood pressure reactivity with exercise (Sprick et al., 2019).

Considering that α1-adrenergic receptors are the primary mediators of vasoconstriction in response to catecholamines, BFRT has been shown to significantly increase plasma concentrations of adrenaline over similar free flow exercise (Takano et al., 2005; Madarame et al., 2008; Shimizu et al., 2016; Sprick et al., 2019). Patients with CKD already present a more remarkable rise in norepinephrine levels during exercise than controls and an exaggerated rise in SBP during moderate static handgrip compared to controls (Kettner et al., 1984; Park et al., 2008). Therefore, the acute increase in noradrenaline for CKD patients with additional cardiovascular comorbidities needs careful attention as an exaggerated exercise pressor response could predispose this population to increased risk of negative cardiovascular events (Spranger et al., 2015; Cristina-Oliveira et al., 2020).

Although BFRT in chronic kidney disease (CKD) is a promising strategy to improve physical functioning and medical management of the condition, there exist some potential concerns regarding the widespread application of BFRT in Stage III/IV CKD patients. However, BFRT in end-stage renal disease, stage two CKD patients, hypertensive patients in stage II CKD, and patients on hemodialysis (Cardoso et al., 2020; Dias et al., 2020; Correa et al., 2021a,b) appear to display no adverse effects. Of note, all included CKD studies present stringent exclusion criteria (e.g., cardiovascular events in the last 3 months, acute infection, neoplastic process, pregnancy, inadequate blood pressure control displayed by SBP above 180 mmHg and/or DBP above 105 mmHg, heart rate above 120 bpm during hemodialysis, decompensated patients, diabetes mellitus, symptomatic heart failure; history of nephrolithiasis or coagulation, human immunodeficiency virus infection, surgery within the past 3 months, drug or alcohol abuse, pre-exercise BP above 160/100 mmHg, previous diagnosis of coronary artery disease, and admission to an intensive care unit).

Considering this, we encourage using **Tables 3–6** for safety purposes and previous critical contraindications to exercise for CKD patients as electrolyte abnormalities, recent changes in the electrocardiogram, excess of inter-dialytic weight gain $>$ 4 kg since the last dialysis or exercise session, unstable on dialysis treatment, changing medication regime, pulmonary congestion, and peripheral edema (Smart et al., 2013). It is important to emphasize that clinicians must ensure that BFRT exercises be individualized to the patient with CKD's current stage of physical ability. Patients in long-term dialysis are more prone to intense pain, musculoskeletal disorders, fragility fractures, and stable angina (Fry et al., 2008; Chan et al., 2009; Heaf et al., 2012). Thus, these patients should be gradually exposed to BFRT. With continued follow-up monitoring and application adjustments along the way (Rolnick et al., 2021) to reduce attrition secondary to increased perceptual and hemodynamic demands, patients with CKD can likely expect to improve their overall health and functionality with longitudinal BFRT programs. Collectively, the complexity and profound variability in CKD highlights the need to include multidisciplinary teams working to optimize individualized BFR management and determine the best progressions to maximize function and medical status.

ANABOLIC STEROIDS, ERGOGENIC SUBSTANCES, AND BLOOD FLOW RESTRICTION TRAINING

In bodybuilders and those pursuing physique-related sports, the literature demonstrates the potential applicability of BFRT. Two recent reviews have highlighted the theoretical benefits of BFRT in bodybuilders during resistance and aerobic training during contest preparation (Rolnick and Schoenfeld, 2020a,b). While the use of anabolic steroids (AS) appears to be higher in those pursuing physique-related endeavors (Haerinejad et al., 2016), AS use has been reported in high

school athletes (Windsor and Dumitru, 1989) and men aiming to improve body image (Kanayama et al., 2020) indicating that AS use is not just for bodybuilding. However, AS use increases the likelihood of adverse effects such as dyslipidemia, polycythemia, hyperhomocysteinemia, a hypercoagulability state, cardiac and vascular hypertrophy, ventricular arrhythmias, impaired angiogenesis, redox balance, arterial hypertension, and cardiomyocyte apoptosis (Patane et al., 2020; Seara et al., 2020). Also, it appears that the long-term effects of AS may not be reversible (Seara et al., 2020), increasing risk during BFRT despite cessation and their apparently healthy appearance.

In addition, most AS users tend to use multiple substances at once, causing synergic effects and systemic disorders whose cause cannot be readily identified by the clinician (Pope et al., 2014). The use of AS combined with other compounds like thyroid hormones, growth hormone, insulin, diuretics, caffeine, yohimbine, and sympathomimetics products (e.g., ephedra alkaloid-containing products) (Cimolai and Cimolai, 2011; Mancano, 2015; Spranger et al., 2015; Seara et al., 2020) may enhance the concern of integrating BFRT into a strength training program by increasing risk of adverse events. Although BFRT appears to be a feasible strategy for maximizing hypertrophy gains in bodybuilders during the pre-contest period, these athletes enter a negative energy balance and dehydration linked to restrictive diets (Alves et al., 2020). The same strategy of negative energy balance occurs in other sport disciplines associated with pre-contest periods, such as in Taekwondo (Rhyu et al., 2014). Such strategies might initiate negative mood alterations, autonomic deregulation, compromised force-generating capacity, as well as elevations in cortisol and reductions in testosterone levels (de Moraes et al., 2019). Moreover, the pre-contest period might induce damage to cell components and greater severity of upper respiratory tract infections from an increase of inflammatory mediators and pro-oxidant markers (Fry et al., 2008).

Recently, a study showed that severe restriction energy intake during the pre-contest period was associated with an increase in oxidative stress markers (TBARS, malondialdehyde and protein carbonyls), impaired upregulation of antioxidant enzymes (glutathione reductase, catalase activity, and superoxide dismutase), and decreased plasma total antioxidant capacity (Rhyu et al., 2014; de Moraes et al., 2019). Moreover, a previous study revealed that during the pre-contest preparation period, different strategies (AS, clenbuterol, thyroid hormone, and ephedrine) might result in maladaptive effects on the lipid profile and alteration of transaminases, increasing the atherosclerotic heart disease risk and liver dysfunction (de Souza et al., 2018). Thus, these adverse effects must be considered in critical periods of bodybuilder preparation (pre-contest) because the underlying systemic changes may potentiate the possible adverse responses related with BFRT.

Furthermore, adverse events associated with ergogenic aids (e.g., dietary supplements) should be considered in the screening process (Geller et al., 2015). Weight loss supplements are implicated in up to 25% of emergency department visits (e.g., palpitations, chest pain, tachycardia, syncope, headache) followed by energy supplements (Geller et al., 2015). Besides, per year females visit the emergency department almost three times that of male patients. In addition, stimulants found in dietary supplements as 1,3-dimethylamylamine, ephedra, β-methylphenethylamine, N,α-diethyl-phenylethylamine, N-caffeoyldopamine, and N-coumaroyldopamine are associated with potential adverse reactions including arrythmias and myocardial infarction and should be considered in screening (Cohen, 2014).

Creatine is another frequently used weightlifting supplement that may heighten risk of adverse events as some published case reports displayed associations between creatine supplementation and venous thrombotic events (Mancano, 2014; Tan et al., 2014; Moussa and Chen, 2021). The possible explanations include osmotic changes secondary to increased intracellular creatine, drawing water into the muscle (Mancano, 2014). This could lead to dehydration, especially in hot environments and cases of heat stroke have been reported among users (Tan et al., 2014). Thus, use of creatine supplementation and the practice of dehydration and electrolyte manipulation in the final days prior to competition and use of BFRT may represent a concern given reported outcomes in the literature. However, no creatine-related adverse events have been reported in the literature either in healthy non-bodybuilders or bodybuilders.

Therefore, the information mentioned above only provides context to potentially relevant precautions when weighing the safety risk for BFRT. Differences due to administration dosage, pattern, and the use of several AS, and ergogenic substances, simultaneously must be accounted for before BFRT, and likely a pre-screening question could aid in this determination.

The decision to use BFRT is based on carefully weighing the evidence for adverse events and providing the safest course of action. A complete blood count and a comprehensive metabolic panel including red and white blood cells, lipid profile, platelets, D-dimer, and fibrinogen can be especially relevant for screening to review the overall health of individual (if within scope of practice) before inclusion of BFRT, especially if AS and/or ergogenic substances use is suspected.

POST-SURGERY AND BLOOD FLOW RESTRICTION TRAINING

When to begin BFRT in the post-surgical patient is one of the most important clinical questions needed to be answered given the rapid effects of disuse on skeletal muscle mass, strength, and cardiovascular capacity. Some studies have shown the safety of the BFRT at various time intervals as early as 2 days post-surgery (Iversen et al., 2016). A previous study demonstrated safety in rehabilitation 2–3 weeks after anterior cruciate ligament surgery using BFRT (Hughes et al., 2019). Another study applied BFRT 3 weeks post- knee arthroscopy surgery (Tennent et al., 2017). One author group has had such success with BFRT that they apply BFRT to all major post-surgical knee patients after 3 weeks (Noyes et al., 2021).

Even with these findings, the use of BFRT following surgery must be carefully analyzed. The risk of DVT is increased 100-fold in the first 6 weeks following surgery (Bond et al., 2019) and

pulmonary embolism risk is more significant in the 12 weeks following surgery in middle-aged women, which of course, will depend on the type of surgery (Sweetland et al., 2009). The relative risk for thrombosis after hip and knee arthroplasty is 220 times higher in the first 6 weeks after surgery, 91.6 times higher after cancer surgery, and 87 times higher after vascular surgery highlighting that surgery of any kind increases risk of DVT formation (Sweetland et al., 2009).

Therefore, we recommend caution when using BFRT post-surgery with and without the use of thromboprophylaxis. Risk will also be modified based on the health status of the patient and any relevant comorbidities (e.g., diabetes mellitus, hypertension, or cardiovascular disease). Clinicians are recommended to screen for DVT from the modified Caprini thrombosis risk factor assessment or IMPROVE scale (Motykie et al., 2000; Caprini, 2005; Rosenberg et al., 2014; Golemi et al., 2019) with any post-surgical patient. The reader is referred to Bond et al. (2019) for a more in-depth look at the post-surgical risk of acquiring a DVT with BFRT.

PATIENTS WITH COVID-19 AND BLOOD FLOW RESTRICTION TRAINING

Patients with COVID-19 that underwent mechanical ventilation likely have intensive care unit-acquired weakness and present with muscle degradation/atrophy (Barbalho et al., 2019; Lad et al., 2020). The changes seen in patients with critical illness myopathy that lead to intensive care unit-acquired weakness include severe muscle atrophy that affects both type I and type II fibers, along with preferential and significant loss of thick filament myosin protein, sarcomere disorganization and electrical hypoexcitability (Lad et al., 2020). Previous studies raised the possibility of using BFRT to counteract severe muscle atrophy and low muscle strength post-intensive care unit, possibly being able to provide a therapeutic alternative approach to traditional rehabilitation (Lad et al., 2020; Roman-Belmonte et al., 2020). Another study displayed that BFRT was able to reduce the magnitude of the rate of muscle wasting in elderly coma patients admitted to the intensive care unit (Barbalho et al., 2019). The 11-day protocol consisted of passive mobilization of 3 sets of fifteen repetitions of knee flexion-extension (at 80% of AOP) at a 2-s flexion/2-s extension cadence and was performed daily throughout the patient's hospitalization. Thus, BFRT might be an essential aid for patients with COVID-19 admitted to the intensive care unit to prevent excessive muscle wasting (Barbalho et al., 2019). However, patients with recent COVID-19 infection display several laboratory abnormalities and thromboembolic complications such as elevated D-dimer, platelets activation, elevated levels of vWF, hyperviscosity and fibrinogen in the blood during the early stages of infection compared to healthy controls (Gupta et al., 2020). Also, alveolar-capillary microthrombi are 9 times more prevalent in individuals with COVID-19 than in those with influenza (Ackermann et al., 2020).

These hemostatic and inflammatory changes reflect endothelial damage. Further, COVID-19 is associated with harmful effects on many other organ systems such as heart, renal, dermatological, neurologic, renal, hepatic, endocrine, and gastrointestinal (Gupta et al., 2020). These systemic changes indicate a pro-inflammatory state and likely elevated risk for clotting. Risk of DVT appears high in patients with COVID-19, and intensive care unit patients with severe COVID-19 infections have been shown to have higher incidences of DVT compared to patients admitted in the general wards (Sarkar et al., 2021). The clinician must also be aware that patients with COVID-19 display common comorbidities as hypertension, DM, and cardiovascular disease (Huang et al., 2021). Hence, previous risks assessment models as **Tables 2–6** should be used with these patients.

The information as mentioned earlier suggests that clinicians should consider (if available) (Gupta et al., 2020):

- ☐ Disease severity: (1) not admitted to hospital with resumption of normal activities; (2) not admitted to hospital, but unable to resume normal activities; (3) admitted to hospital but not requiring supplemental oxygen; (4) admitted to hospital but requiring supplemental oxygen; (5) admitted to hospital requiring high-flow nasal cannula (HFNC), non-invasive mechanical ventilation (NIV), or both; (6) admitted to hospital requiring extracorporeal membrane oxygenation, invasive mechanical ventilation (IMV) (Huang et al., 2021).
- ☐ Inflammatory markers: elevations in erythrocyte sedimentation rate, C-reactive protein, ferritin, IL-6, lactate dehydrogenase.
- ☐ Coagulation indices: elevated D-dimer and fibrinogen; prolonged prothrombin time and partial thromboplastin time.
- ☐ Consider if the patient used thromboprophylaxis post-hospitalization, particularly for those with a history of critical illness.

As these are not frequently known by the patient presenting to outpatient rehabilitation, collaborating with a referring physician is advised to determine if these values exceed normal. Finally, the clinician should have working knowledge and understanding of COVID-19 to mitigate risk using BFRT in this population. More studies are needed to make stronger BFRT recommendations with a sufficient degree of confidence.

APPARENTLY HEALTHY INDIVIDUALS AND BLOOD FLOW RESTRICTION TRAINING

Most studies involving BFRT are published using apparently healthy individuals (Moriggi et al., 2015). Thus, considering the absence of adverse responses, the risk stratification includes the following items (**Table 7**).

Use of Caprini's thrombosis risk factor assessment and modified IMPROVE risk score (Motykie et al., 2000; Caprini, 2005; Spyropoulos et al., 2011; Mahan et al., 2014; Rosenberg et al., 2014; Golemi et al., 2019; **Tables 2**, **3**) should also be integrated into the screening process in conjunction with risk factors cited in **Table 7**. When in doubt, the clinician is advised to consult with other clinician experts/physicians to determine appropriate BFRT candidacy (Rolnick et al., 2021).

TABLE 7 | Risk factors concerning apparently healthy individuals before BFRT.

Patient's Name:_____
Age:_____
Sex:_____

In the presence of any items in the list below, BFR training should be avoided.
☐ Self-reported easy bruising (Ballas and Kraut, 2008);
☐ Acute systemic illness;
☐ A medical problem that the physician and BFR practitioner believes may be life-threatening;
Note: For apparently healthy individuals with < 2 (low cardiovascular risk) factors[a]. BFR training may be considered safe.

[a]*Men ≥ 55 years or women ≥ 65 years; History of premature CVD in 1st degree relatives: men < 55 years old or women < 65 years old; Smoking; Dyslipidemia: total cholesterol > 190 mg/dL and/or LDL-cholesterol > 115 mg/dL and/or HDL-cholesterol < 40 mg/dL in men or < 46 mg/dL in women and/or Triglycerides > 150 mg/dL; Insulin resistance: fasting plasma glucose between 100 and 125 mg/dL, oral glucose tolerance test between 140 and 199 mg/dL in 2 h, glycated hemoglobin between 5.7 and 6.4%; Obesity: BMI ≥ 30 kg/m^2, waist circumference ≥ 102 cm for men or ≥ 88 cm for women. Adapted from previous studies (Fletcher et al., 2001; Milech et al., 2016; Diabetes, 2019; Mach et al., 2020; Pelliccia et al., 2021).*

DISCUSSION

The danger associated with not exercising is more significant than that associated with exercising (Pedersen and Saltin, 2006), but the results of the studies displayed till now highlight that BFRT should be carefully implemented. The authors of this manuscript are aware that not all individuals can perform heavy load strength training and thus the clinician may decide to use with BFRT after evaluating risk factors. In that case, we recommend that coagulation indices as safety issues for DVT before and after regular BFRT and blood pressure monitoring be frequently analyzed if possible. We also recommend some criteria adapted from a previous study that can be used to stop training during BFRT (Fletcher et al., 2001; O'Brien et al., 2018):

- Development of significant ventricular or atrial arrhythmias.
- The onset of chest pain/discomfort, or other symptoms, suggestive of myocardial ischemia.
- Dizziness, confusion, deteriorating balance, or other significant neurological symptoms.
- Paleness or cyanosis.
- Vomiting, nausea, or feeling generally unwell.
- Decrease in systolic blood pressure from rest < 10 mmHg in the absence of symptoms.
- Hypertensive systolic blood pressure ≥ 250 mmHg and or diastolic blood pressure ≥ 115 mmHg.
- Exhaustion or fatigue (malaise), sometimes persisting for days, that is out of keeping with the person's usual response to exercise at a given intensity.
- Swelling and shortness of breath.
- Skin of the affected limb that is too hot or cold to touch.
- Increased/excessive pain in the affected limb.
- Excessive discoloration of the affected limb.
- Subject requests to stop.

Clinicians that will use the proposed risk stratification in this manuscript should have education and training in pathological states and their significance to the BFRT response in both resistance and aerobic training approaches. Education and training can come from curated post-professional BFR courses or self-study. Both are likely very important to reduce risk of improper application of BFRT that may increase risk of adverse events and liability.

The *American Physical Therapy Association* defines scope of practice for physical therapists using a threefold definition: professional, jurisdictional, and personal (APTA, 2020). While jurisdictional scope of practice is regionally defined and professional scope is determined through accreditation and the licensing process to become a physical therapist, personal scope of practice is achieved through activities that the clinician is educated and trained on and is competent to perform. With respect to BFRT, competency likely includes knowledge of typical BFRT responses to exercise, characteristics of BFRT devices and ability to apply BFRT according to established guidelines. Thus, just because BFRT is within the scope of practice of physical therapists does not itself demonstrate competency to safely perform (CA.GOV, 2005).

The proposed risk stratification is not yet backed up by specific data regarding the clinical benefit and cost-effectiveness of BFRT. Hence, the risk stratification proposed herein reviews adverse effects displayed by data derived from expert opinions, small studies, randomized clinical trials, and non-randomized studies. Nevertheless, the proposed stratification risk score should be externally validated to demonstrate if it can be used with reproducible accuracy and confidence to ensure appropriate patient care before BFRT. However, we believe that this risk stratification assessment may represent a useful initial effort aimed at minimizing adverse responses in the clinical setting for clinicians looking to improve rehabilitation and fitness outcomes in their patients. The proposed risk stratification application into practice is not likely to be very long and cumbersome to complete (e.g., taking minutes to integrate). However, shorter risk stratifications have the obvious advantage of brevity and provide sufficient information on relative risk. Future risk stratification questionnaires can build upon the proposed risk factors in each condition to further reduce potentially redundant criteria such as in the IMPROVE scale (Rosenberg et al., 2014) to stratify the primary risk factors determined through longitudinal research. However, the lesson to be drawn from efforts to derive reliable and valid stratification risks is that substantial empirical work is needed to ensure that proposed risk stratifications operate as intended.

Finally, the authors attempted to summarize the strength of the available scientific evidence underlying BFRT observed in the various subsections of this narrative review. However, traditional narrative reviews and systematic reviews differ in several ways. Systematic reviews attempt to minimize bias by assessing the methodologic quality of included studies, inclusion and exclusion criteria, validity, and so forth (West et al., 2002). Significant challenges arise when evaluating the strength of evidence in a body of knowledge comprising combinations of observational and randomized clinical trial data (West et al., 2002). No single approach is ideally suited for assessing the strength of scientific evidence, particularly in cases where evidence is drawn from various methodologies (West et al., 2002). Considering that BFRT is a modality with growing interest in the last decade, especially for clinical patients, it would be too soon to summarize the strength of evidence for each subsection described within this manuscript. Furthermore, systematic reviews have a broad search and coding protocol to attend to a specific and narrow scope. Unlike narrative reviews, systematic reviews do not cover a broad topic that involves multiple independent variables with multiple and distinct outcomes. A narrative review does not use the systematic search and analytic protocols as a systematic review although it can cover a broader research topics hidden by multiple outcomes that follow BFRT intervention. This type of research is relevant to elucidate mechanisms and suggest potential gaps for further investigation in BFRT.

CONCLUSION AND PERSPECTIVES

Clinicians should use judgment, knowledge of relevant risk factors, clinical experience, and in some cases, common sense to provide adequate screening and monitoring when administering BFRT. In the final analysis, the inclusion to use BFRT is based on carefully weighing the evidence for adverse events and providing the safest course of action for the patient, allowing for optimization and better planning of care. Therefore, a risk stratification is likely essential for the start of a safe and effective BFRT program and can help in the decision-making process for all clinicians.

A useful BFRT risk stratification goes beyond the individual's classification risk as it also allows the clinician to direct the therapeutic approach, establish a level of monitoring and the determine the appropriate dose of exercise. These proposed adapted risk stratifications can help in the screening process, removing barriers to initiating BFRT programs for clinicians in all settings. Finally, the risk stratification might serve as a guideline for clinical protocols and future randomized controlled trial studies.

AUTHOR CONTRIBUTIONS

DN and NR conceived, designed the study, and conducted the reference review. DN, NR, IN, RS, and FB contributed to the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: NR is the founder of THE BFR PROS, a BFR education company that provides BFR training workshops to fitness and rehabilitation professionals across the world using a variety of BFR devices. NR has no financial relationships with any cuff manufacturers/distributors.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Exercise With Low-Loads and Concurrent Partial Blood Flow Restriction Combined With Patient Education in Females Suffering From Gluteal Tendinopathy: A Feasibility Study

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Introduction: To date, there exists no gold standard conservative treatment for lateral hip pain due to tendinopathy of the gluteus medius and/or minimus tendon (GT), a condition often complicated by pain and disability. Higher loads during everyday activities and exercise seems to be contraindicated with GT. The purpose of this study was to evaluate the feasibility of exercise with low-loads concurrent partial blood flow restriction (LL-BFR) and patient education for patients present GT.

Methods: Recruitment took place at three hospitals in the Central Denmark Region. The intervention consisted of daily sessions for 8 weeks with one weekly supervised session. From week three patients exercised with applied partial blood flow restriction by means of a pneumatic cuff around the proximal thigh of the affected leg. Throughout the intervention patients received patient education on their hip condition. Sociodemographic and clinical variables were collected at baseline. The feasibility of LL-BFR was conducted by adherence to the exercise protocol and drop-out rate. Patient reported outcome measures (The Victorian Institute of Sport Assessment-Gluteal Questionnaire, EuroQol - 5 Dimensions-Visual Analogue Scale, Oxford Hip Score, Copenhagen Hip and Groin Outcome Score), maximal voluntary isometric hip abduction-, hip extension, and knee extension strength (Nm/kg) measured using a handheld dynamometer, and functional capacity tests (30 second chair-stand test and a stair-climb test) was conducted as secondary outcomes.

Results: Sixteen women with a median (IQR) age of 51 (46–60) years were included. Median (IQR) Body Mass Index was 26.69 (23.59–30.46) kg/m2. Adherence to the total number of training sessions and the LL-BFR was 96.4 and 94.4%, respectively. Two patients dropped out due to (i) illness before initiation of LL-BFR and (ii) pain in the

affected leg related to the LL-BFR-exercise. At follow-up both pain levels and patient-reported outcome measures improved. Isometric hip abduction-, hip extension-, and knee extension strength on both legs and functional performance increased. Conclusion: LL-BFR-exercise seems feasible for treatment of GT. At follow-up, a high adherence and low drop-out rate were observed. Further, patients reported clinically relevant reductions in pain, and showed significant increases in isometric hip and knee strength.

Keywords: blood flow restriction, feasibility, patient education, venous occlusion, exercise therapy, gluteal tendinopathy

INTRODUCTION

Gluteal tendinopathy (GT) of the hip abductor muscle tendons (gluteus medius and minimus) has recently been recognized as the primary underlying pathology causing greater trochanteric pain syndrome (Kagan, 1999; Kingzett-Taylor et al., 1999; Bird et al., 2001; Kong et al., 2007; Fearon et al., 2010; Grimaldi and Fearon, 2015). The patient population primarily consists of females aged 40–60 years (Grimaldi et al., 2015). Recent studies indicate that GT is among the most prevalent lower limb tendinopathies in adults seen in general practice and is associated with moderate to severe hip-related pain and disability (Fearon et al., 2014; Albers et al., 2016; Riel et al., 2019; Bohn et al., 2021). GT presents pain directly above the greater trochanter (Grimaldi and Fearon, 2015; Speers and Bhogal, 2017). Further, stair climbing, sleeping on the symptomatic side, and walking have been reported by patients with GT to aggravate pain (Woodley et al., 2008).

Several conservative treatment strategies have been recommended for patients suffering from GT, i.e., rest, shock-wave therapy, and corticosteroid injections (Brinks et al., 2011; Mellor et al., 2018; Ramon et al., 2020). However, to our best knowledge none of the previous treatment modalities promoted long lasting effects on patient reported function and/or pain (Brinks et al., 2011; Mellor et al., 2018; Ramon et al., 2020). Interestingly, low-load exercises performed daily combined with patient education have been observed to be superior to corticosteroid injections and a "wait and see" approach on patient reported global improvement and hip pain intensity 1 year after the intervention in patients with GT (Mellor et al., 2018). However, a high-frequent low-load exercise regimen to reduce symptoms is in sharp contrast to the literature on other lower limb tendinopathies (Kongsgaard et al., 2009; O'Neill et al., 2015). In clinical practice it is consistently reported that patients report severe pain exacerbations when moderate-to-high exercise loads are applied and/or the total training volume is progressed too fast. Therefore, low-load exercise regimens are highly warranted for this patient population.

Low-load exercises with concurrent restriction of the blood flow by means of a pneumatic cuff placed on the proximal part of the exercising extremity (LL-BFR) has consistently demonstrated promotion of skeletal muscle hypertrophy and increase strength in both patients and healthy individuals (Hughes et al., 2017; Lambert et al., 2018). Additionally, LL-BFR has been observed to increase muscle strength to the same extent as heavy load resistance strength training (Grønfeldt et al., 2020).

Recent studies indicate that LL-BFR may improve tendon morphology in both patients and healthy individuals (Sata, 2005; Centner et al., 2019; Skovlund et al., 2020). That is, LL-BFR has demonstrated to increase blood lactate level (Reeves et al., 2006; Manini et al., 2012) and stimulate growth hormone secretion, both suggested to contribute to tendon wound healing by upregulating the collagen synthesis (Klein et al., 2001; Yalamanchi et al., 2004; Boesen et al., 2013; Ilett et al., 2019).

To date, no studies have investigated the feasibility of LL-BFR in patients suffering from GT. Interestingly, improvements on skeletal muscle hypertrophy and strength in muscle groups proximal to the cuff have been demonstrated (Abe et al., 2005; Yasuda et al., 2010, 2011; Bowman et al., 2019). Additionally, it has been suggested that LL-BFR may trigger exercise-induced hypoalgesia comparable to levels seen after high intensity exercise (Hughes and Patterson, 2019). Thus, LL-BFR appears to be a relevant exercise treatment for this particular patient population.

The aim of this study was to examine the feasibility of LL-BFR combined with patient education for patients with GT in terms of adherence, dropouts, and adverse events. A secondary purpose was to evaluate changes in lateral hip pain, patient-reported outcomes, functional performance, and hip and knee muscle strength after an 8-week LL-BFR intervention.

MATERIALS AND METHODS

Design

Feasibility study.

Setting

Patients were referred to the study by orthopedic specialists and physiotherapists working in orthopedic outpatient clinics at three public hospitals (Horsens Regional Hospital, Aarhus University Hospital, Silkeborg Regional Hospital).

The intervention and testing took place at two hospitals only (Horsens Regional Hospital and Aarhus University Hospital). The intervention was conducted by two physiotherapists, while one of these (MH) conducted all tests.

Participants

Inclusion criteria were (1) subjective complaints of lateral hip pain, (2) palpable tenderness or pain at the insertion point of the

FIGURE 1 | Cuff placement.

gluteus medius/minimus tendon at the greater trochanter, (3) a positive Single Leg Stance test (SLS), by reproduction of know lateral hip pain within 30 s of one leg stance, (4) lateral hip pain provoked by the FADER (Flexion Adduction External Rotation) and/or the FADER-R (Flexion Adduction External Rotation with resisted isometric internal rotation) test, (5) age 18–75 years and (6) ability to read and understand Danish. The diagnosis was based on the clinical tests described by Grimaldi et al. (2017). Exclusion criteria were (1) corticosteroid injection in the affected hip within the last 6 weeks prior to the intervention (2) any prior surgery in the affected hip (3) unregulated hypertension ($\geq$ 180 mmHg/ $\geq$ 110 mmHg) (4) complaints or clinical signs of bilateral GT (5) MRI or X-ray verified osteoarthritis or (6) pregnancy. See **Supplementary Material** no. 1 for the clinical tests.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki. The study was presented to the ethics committee of Central Region Denmark, who decided that no formal ethical approval was required (record number: 1-10-72-181-20). The Danish Data Protection Agency (record number: 1-16-02-548-20) approved the study and all patients gave written informed consent prior to inclusion.

Intervention

The intervention had an overall duration of 8 weeks and consisted of exercises and patient education. Once a week, exercise sessions were performed at the hospital under supervision of the primary investigator (MH) or a trained physiotherapist (LCUR). Remaining exercises sessions were performed at home without supervision, yielding a total of eight supervised sessions and 48 sessions at home.

At baseline and at eight-week follow-up, patient-reported outcomes, two tests of physical function, isometric hip and knee muscle strength tests were completed.

Exercise Program

The exercises chosen in this study were inspired by a previous study by Mellor et al. consisting of four to six exercises per session (Mellor et al., 2018). However, due to the duration of rest between sets and exercises using LL-BFR, only four exercises per session were chosen for this study. Static abduction, sidestepping, glute bridging, and bodyweight squats were chosen, as these exercises included functional retraining, strengthening of the hip and thigh muscles and control of adduction during function as proposed by Mellor et al. (2018).

Week 1 and 2, each training session consisted of the following: 5 $\times$ 5 s of standing static abduction, side-stepping; 10 steps to each side, 10 repetitions of glute bridging and 10 repetitions of squats. The exercises were to be performed once a day with bodyweight only. From week 3 to 8, static abduction and side-stepping were continuously performed daily. Glute bridging and squats were only performed every second day, and these two exercises were exclusively performed with the application of an 11.7 cm wide pneumatic BFR nylon cuff (Occlude Aps, Denmark) around the affected leg (**Figure 1**).Cuff pressure was 60% of the pressure required to fully restrict blood flow to the exercising limb. Given the relatively low volume in regards of repetitions of the BFR exercises from week 3 to 7, the restriction time was much shorter than suggested by Patterson et al. (5–10 min per exercise) (Patterson et al., 2019). That is, the squat and the bridging exercise combined, would until week 7 only last $\sim$4 min. Thus, in order to reach the proposed restriction time, both the rest between exercises and a 30-s extra period after completion of the exercises were carried out. Given the increased number of repetitions, the participants released the pressure in the pause between the exercises in week 7 and 8. A LL-BFR session progressed from $\sim$15 min in week 3 to $\sim$25 min in the final 2 weeks. Repetitions in double leg bridging, and double leg squats were alternately increased by 10 repetitions every week until patients performed three sets of 20-10-10 repetitions. The full exercise programme with progressions is presented in **Figure 2**. The whole intervention is described according to the Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann et al., 2014) in **Supplementary Material** No. 2. In case of illness during the intervention-period, which would result in absence from a supervised session, the progression for the following week and the patient education was managed by a telephone call. Throughout the intervention-period, patients were required to complete a daily training diary. In addition to reporting the number of repetitions, patients reported their perceived hip-related pain on a Numerical Rating Scale (NRS: 0-10) for every exercise and scored their perceived rating of exertion (RPE: 0-10) for the entire session. Diaries for the previous week were collected at the supervised sessions.

Patient Education

At baseline testing, all patients received written information on the anatomy of the gluteus muscles, common GT-symptoms, pain management, load management, appropriate movement patterns, and resting positions. Patients were encouraged to avoid hip adduction across midline, prolonged single leg stance, lying on the affected side, and to place a pillow between the

Step	Exercise	Repetitions	Sets	Rest between sets	Resistance	Cuff (+/-)
Week 1-2:						
Daily	Static abduction	5 seconds	5	10-15s		-
	Side-stepping	10 pr. side	1			-
	Glute bridging	10	1		BW	-
	Squat	10	1		BW	-
Week 3:						
Daily	Static abduction	5 seconds	5	10-15s		-
	Side-stepping	10 pr. side	1			-
Every second day	Glute bridging	10	1		BW	+
	Squat	10	1		BW	+
Week 4-8:						
Daily	Static abduction	5 seconds	5	10-15s		-
	Side-stepping	10 pr. side	1			-
Week 4:						
Every second day	Glute bridging	10	2	30s	BW	+
	Squat	10	1		BW	+
Week 5:						
Every second day	Glute bridging	10	2	30s	BW	+
	Squat	10	2	30s	BW	+
Week 6:						
Every second day	Glute bridging	10	3	30s	BW	+
	Squat	10	2	30s	BW	+
Week 7:						
Every second day	Glute bridging	10	3	30s	BW	+
	Squat	10	3	30s	BW	+
Week 8:						
Every second day	Glute bridging	20-10-10	3	30s	BW	+
	Squat	20-10-10	3	30s	BW	+

BW: Bodyweight

FIGURE 2 | Exercise program.

knees during sleep, and rest on the non-affected side to reduce tension and compression of the gluteus medius muscle and tendon. During supervised sessions, patients were continuously educated to manage their GT-symptoms according to the written information received at baseline, and time was taken to verbally instruct and ensure the understanding of the information regarding tendon care and load and pain management.

Measurement of Limp Occlusion Pressure (LOP)

To individualize the cuff pressure during the exercise session, measurement of the pressure required to fully restrict blood flow to the affected lower limb [limp occlusion pressure (LOP)] was determined prior to week 3. A rigid nylon cuff (Occlude Aps, Denmark) with a removable manometer was fitted around the proximal thigh on the affected leg. The posterior tibial artery was located to detect the auscultatory pulse using a vascular doppler probe (EDAN SD3, China). The cuff was gradually inflated until the auscultatory pulse was undetectable as described previously elsewhere (Jørgensen et al., 2020). During LL-BFR exercises a cuff pressure corresponding to 60% LOP was applied and remained constant throughout the entire intervention period. As LOP is affected by body position (Sieljacks et al., 2018), LOP was measured in both seated and supine reflecting the body position of the torso during mini-squats and glute bridging. Subsequently, patients were carefully instructed to apply and inflate the cuff correctly, and further to regulate the pressure between the exercises according to either the mini-squats or glute bridging, without totally deflating the cuff.

Outcome Measures

Feasibility

Adherence was measured as the proportion of exercise sessions completed in relation to the planned exercise sessions. Acceptable adherence was a priori set as a patient completing $\geq$80% of the planned sessions. Drop-out was defined as any reason for failure to continue the intervention and/or complete follow-up tests. Reasons for dropout was noted. A drop-out rate of 15% was considered acceptable. Adverse events were defined as any unexpected pain sensation, musculoskeletal injury, or cancellation of training sessions due to pain associated with the LL-BFR.

Descriptive Measurements

Self-reported bodyweight and height were collected, and body mass index was calculated (kg/m^2). Further, self-reported

TABLE 1 | Baseline characteristics ($n = 16$).

Variable	
Sex, women, *n*	16
Age, years, median (IQR)	51 (45–60)
Height, cm, median (IQR)*	166 (164–169) ($n = 15$)
Weight, kg, median (IQR)*	70 (65–86) ($n = 15$)
Body Mass Index, kg/m^2, median (IQR)	26.96 (23.59–30.46) ($n = 15$)
Affected side, *n* (%)	
Left	8 (50%)
Right	8 (50%)
Occupation status, *n* (%)	
Employed	12 (75)
Unemployed	1 (6.25)
Incapacity benefit	1 (6.25)
Retired	2 (12.5)
Children	
Yes	15 (93.75)
Pain duration, *n* (%)	
<2 months	0
2–6 months	2 (12.5)
7–12 months	3 (18.75)
> 12 months	11 (68.75)
NRS pain, 0–10, mean (SD)	5.43 (1.3)
Cuff-pressure (mmHg), mean (SD)	Seated: 131 (19.5)
	Supine: 116 (24.1)

IQR, Inter Quartile Range; SD, standard deviation; NRS, Numeric rating scale.
**Weight and height were missing for one patient, who was a dropout.*

duration of pain, educational level, marital status, and children (yes/no) were collected.

Patient-Reported Outcomes

Following questionnaires were completed at baseline and follow-up:

(i) The Victorian Institute of Sport Assessment-Gluteal questionnaire (VISA-G) is validated for measuring the severity of disability associated with GT (Fearon et al., 2015). VISA-G is comprised of eight questions and quantifies pain related to GT during loading (score range 0–100), where a higher score indicates less disability and pain.

(ii) The European Quality of Life −5 Dimensions Visual Analogue Score (EQ5D-VAS) is a vertical visual analogue scale (0–100, worst-best) on which the responder scores his/her perception of their overall health at a given day (Balestroni and Bertolotti, 2012).

(iii) The Oxford Hip Score (OHS) is a 12-item patient-reported outcome developed and validated to assess hip pain and function in patients undergoing total hip replacement with a composite score ranging from 0 (worst) to 48 points (best) (Wylde et al., 2005).

iv) The Copenhagen Hip And Groin Outcome Score (HAGOS), is a valid and reliable patient-reported outcome for hip and groin pain in young to middle-aged individuals [score range: 0 (worst) – 100 (best)] (Thorborg et al., 2011). The HAGOS score consists of six separate subscales (pain, symptoms, physical function in daily living, physical function in sport and recreation, participation in physical activities, and hip and/or groin related quality of life).

Pain during exercise in the 8 weeks on a Numerical Rating Scale (NRS) from 0 to 10 (0 = no pain, 10 = worst imaginable pain) was measured. Scores $\leq$ 5 were considered acceptable (Mellor et al., 2016).

Further, at follow-up, patients filled out the Global Rating of Change score (GRoC). GRoC consists of a 11-point scale, where the patient rates the perceived overall change of the hip condition from "very much better" to "very much worse" (Kamper et al., 2009). Responses on GRoC were considered successful if patients scored "moderately better" to "very much better." Global improvement was measured as the percentage of successful reports.

Performance-Based Outcomes

Performance-based function was tested using a 30-s Chair-Stand Test (30s-CST) and a Stair Climb Test (SCT).

The 30s-CST is a test of functional capacity (Alcazar et al., 2020). The patient is seated in a chair with a seat height of 46 cm, and with their feet on the floor, placed shoulder-width apart with the arms crossed across the chest. During the test the patient moves from the sitting position to standing position with the hips at least in neutral position. The tester demonstrates the test prior to the patient's attempt. The patient completes as many stands and sits as possible in 30 s. The number of sits to stand completed in 30 s was recorded by MH.

Stair ascending (SCT) is a low-cost test used to estimate muscle power output (Cormie et al., 2011) (se calculation below). In this study, the patients were instructed to ascend a flight of stairs as fast as possible comprising of 11 steps with a total distance of 7.46 meters. A timer was started at the tester's command at the base of a staircase and stopped when the patient reached the top of the staircase with both feet on the last step. This time in seconds was then transformed into watts by the following formula used in (Novoa et al., 2015):

$$\frac{bodyweight\,(kg) \times 9.8 \times altitude\ ascended\,(m)}{time\ taken\,(s)} = Power\,(W) \quad (1)$$

Muscle Strength

Maximal voluntary isometric contraction (MVIC) was measured using a handheld dynamometer (HHD) (JTech Commander PowerTrack Muscle Dynamometer MMT, USA).

Isometric hip abduction (MVIC HA) was performed following a previously described test protocol (Kemp et al., 2013), i.e. with the patient lying supine on an examination bed while the patient's foot was resting on the examination bed. The HHD was placed 5 cm above the lateral malleolus. With the non-testing leg fixated with a belt around the table, the patient was instructed to push as forcefully as possible into the HHD while maintaining full hip and knee extension. The patient was given 3 trials on each limb.

TABLE 2 | Patient-reported outcomes ($n = 14$).

Outcome	Baseline mean [95% CI]	Follow-up mean [95% CI]	Mean change [95% CI]	*p*
Pain (NRS, 0–10)	5.43 [4.65;6.20]	2.71 [1.82;3.60]	−2.71 [−3.71; −1.72]	<0.001
VISA-G (0–100)	56.57 [50.26;62.89]	66.57 [57.04;76.10]	10 [0.20;19.80]	0.046
EQ5D-VAS (0–100)	68.36 [59.69;77.02]	80 [72.84;87.16]	11.64 [3.33;19.96]	0.009
Oxford hip score (0–48)	29 [24.75;33.25]	36.6 [32.86;40.37]	7.6 [4.57;10.66]	<0.001
HAGOS (0–100)				
Symptoms	49.75 [43.00;56.49]	69.90 [58.85;80.95]	20.15 [9.47;30.83]	0.001
Pain	53.39 [44.47;62.32]	69.82 [58.99;80.64]	16.43 [6.61;26.25]	0.003
ADL	55.71 [46.74;64.69]	70 [55.59;84.41]	14.29 [3.73;24.84]	0.011
Sports/Rec	40.85 [30.19;51.49]	59.82 [44.16;75.49]	18.97 [6.38;31.56]	0.006
PA	33.93 [19.38;48.48]	41.07 [22.20;59.94]	7.14 [-10.47;24.76]	0.397
QOL	31.43 [25.39;37.47]	45.00 [31.94;58.06]	13.57 [1.78;25.36]	0.027

VISA-G, Victorian Institute of Sport Assessment-Gluteal; EQ5D-VAS, European Quality of Life - 5 Dimensions - Visual Analogue Scale; NRS, Numeric rating scale; HAGOS, Copenhagen Hip and Groin Outcome Score; ADL, Function in daily living; Sports/Rec, Function in sport and recreation; PA, Participation in Physical Activities; QOL, Hip and/or groin-related Quality of Life.

TABLE 3 | Performance-based outcomes and isometric muscle strength ($n = 14$).

Outcome	Baseline (mean [95% CI])	Follow-up (mean [95% CI])	Mean change (baseline-Follow-up) mean [95% CI]	*p*	Diff. of change between legs (Follow-up), mean [95% CI]	*p*
30s-CST, no of reps	14.6 [12.2;17.1]	19.4 [16.3;22.4]	4.7 [2.9;6.5]	<0.001		
SCT, Watt	282.61 [247.16;318.05]	334.99 [289.88;380.12]	52.39 [12.62;92.16]	0.014		
MVIC, Hip abduction, Nm/kg,						
Affected leg	0.81 [0.67;0.96]	1.02 [0.87;1.17]	0.21 [0.11;0.31]	<0.001	0.10 [0.03;0.18]	0.012
Non-affected-leg	0.99 [0.85;1.12]	1.09 [0.95;1.23]	0.10 [-0.02;0.23]	0.083		
MVIC, Hip, extension, Nm/kg						
Affected-leg	0.43 [0.34;0.53]	0.70 [0.55;0.86]	0.27 [0.15;0.39]	<0.001	0.08 [-0.01;0.16]	0.067
Non-affected-leg	0.53 [0.40;0.65]	0.72 [0.57;0.86]	0.19 [0.13;0.24]	<0.001		
MVIC, Knee extension, Nm/kg						
Affected—leg	1.05 [0.80;1.30]	1.26 [0.97;1.56]	0.21 [0.02;0.40]	0.031	0.10 [-0.01;0.20]	0.061
Non-affected-leg	1.16 [0.93;1.38]	1.27 [1.00;1.54]	0.11 [-0.02;0.25]	0.085		

30s-STS, 30 second sit-to-stand; SCT, Stair Climb Test; MVIC, Maximal Voluntary Isometric Contraction.

Isometric hip extension (MVIC HE) followed the protocol in the study by Kemp et al. (2013). Briefly, MVIC HE was performed with the patient lying prone on an examination bed, the examined knee flexed 90° and the HHD placed on the heel. The patient was instructed to push as forcefully as possible, upwards into the HHD, trying to lift the knee and thigh free of the surface of the examination bed. The patients were given 3 trials on each limb.

Isometric knee extension (MVIC KE) was measured with the patient seated with both hip and knees positioned in 90° flexion, with the feet hanging over the edge of the examination bed. The HHD was placed 5 cm above the lateral malleolus, anterior to the tibia, on a shin guard strapped around the patient's shin. This was a slight modification to the protocol (Koblbauer et al., 2011), which used the medial malleolus as fixation point instead. To keep the HHD in position, a strap was attached to the examination bed, long enough to keep the patient's knee flexed at 90° during the test. The patient was instructed to kick/push as hard as possible into the HHD. Three trials on each limb were given.

Statistical Analysis

Baseline characteristics were described using numbers (n), proportions (%) for categorical data, and mean and standard deviations (SD) for continuous data if the values were normally distributed. Otherwise, median and interquartile range (25th−75th percentiles) were presented.

Adherence was calculated as the proportion of completed exercise sessions for both the overall number of sessions and for the LL-BFR-sessions alone. Formula used to calculate

the adherence:

$$\frac{\left(\frac{Total\ exercise\ sessions\ completed}{Total\ weeks\ completed}\right)}{Number\ of\ weekly\ exercise\ sessions\ scheduled} \times 100 = Adherence\ (\%) \quad (2)$$

Changes in secondary outcome measures from baseline to follow-up were evaluated by using paired t-tests given the data were normally distributed, otherwise a Wilcoxon signed-rank test was used. Level of significance was set at 5%. Stata 16.0 (Statacorp, Texas, TX USA) was used for the statistical analysis. Proportion (%) of successful global improvements was presented using descriptive statistics.

RESULTS

Eligible Patients

The study was conducted from October 2020 to April 2021. Sixteen females were included, and 14 completed the intervention. Baseline characteristics are presented in **Table 1**. Two patients had their intervention period extended from 8–9 weeks (one due to COVID-19, and one due to excessive hip-related pain at the time of initiation of LL-BFR).

Feasibility and Adherence

The mean (SD) adherence to all exercise sessions was 96% (5.76), with the patient with the lowest adherence displaying an adherence of 79%. The mean (SD) adherence to the LL-BFR-sessions only was 94% (8.52), with the patient with the lowest adherence achieving an adherence of 72%. One patient dropped out due to illness prior to the initiation of the LL-BFR. Another withdrew due to excessive pain during LL-BFR at home.

Adverse Events

One adverse event, leading to a drop out, was registered during the intervention. The patient experienced a sudden and ongoing pain sensation during a LL-BFR session. The intensity of the pain was reported as 8-9 NRS. The pain was located directly beneath the LL-BFR-cuff and radiating throughout the leg alongside the affected leg. The patient counselled her general practitioner who advised her to stop her participation in the study. Two weeks later, the patient reported to have resumed her daily exercise sessions without the LL-BFR-cuff and did not experience pain with exercise.

Patient-Reported Outcomes

Patient-reported hip pain, function, and quality of life from baseline to follow-up are presented in **Table 2.** Overall mean lateral hip pain (NRS) decreased significantly. Both VISA-G, EQ-5D-VAS, OHS and the majority of the subscales in HAGOS (5 out of 6) improved significantly. Nine out of 14 patients (64%) reported successful improvements on the GRoC. Mean (SD) hip pain during exercise throughout the intervention-period was 2.20 (1.43).

Performance-Based Outcomes

The mean number of repetitions in the 30s-CST as well as the mean power output in the SCT increased significantly from baseline to follow-up (**Table 3**).

Isometric Muscle Strength

Isometric muscle strength outcomes are presented in **Table 3**. Significant improvements of isometric strength were seen in the affected leg in both MVIC HA and MVIC KE, and in both legs in MVIC HE. The difference in strength change between the affected and unaffected leg was only significant in MVIC HA.

DISCUSSION

The main finding of this study was that 8 weeks of LL-BFR and patient education was feasible in the included female population suffering from GT. In general, adherence to the exercise intervention was high (96%) and the drop-out rate low (13%). Only one patient dropped out due to LL-BFR related pain exacerbation. Additionally, LL-BFR was performed without an augmented pain sensation. At follow-up, a clinically relevant reduction in lateral hip pain and improvements of both patient-reported outcomes, functional capacity and isometric muscle strength were seen.

Feasibility Outcomes

In the present study we observed an exercise adherence corresponding to 96%, which is higher than the adherence previously reported with daily exercise sessions planned for patients suffering from GT (Ganderton et al., 2018; Mellor et al., 2018). Mellor et al. reported a mean (SD) adherence at 88.8% (13.7) after 8 weeks of daily home-based/supervised low-load exercise intervention (Mellor et al., 2018). Ganderton et al. reported an adherence corresponding to 75.80% (23.49) for the intervention group after 12 weeks of a low-load exercise and 75.99% (25.35) for the control group, engaging in 12 weeks of a sham exercise involving primarily seated exercises with no external load (Ganderton et al., 2018). Recently, other homebased LL-BFR exercise protocols have emerged and demonstrated excellent adherence when applied in clinical populations (Kilgas et al., 2019; Petersson et al., 2020; Jørgensen and Mechlenburg, 2021). Both Petersson et al. (2020) and Jørgensen and Mechlenburg (2021) have reported adherence of 100% to a 5-week combined homebased and supervised BFR walking exercise protocol (three sessions/week, one of these supervised) in a patient suffering from knee OA and to a 12-week homebased LL-BFR intervention (exercise session every second day, supervision only during the first week) in a patient suffering from reactive arthritis, respectively (Petersson et al., 2020). In line with this, Kilgas et al. reported an adherence of 100% to a 4-week entirely homebased LL-BFR intervention (40 sessions in total) in a patient who had received a total knee arthroplasty (Kilgas et al., 2019). Thus, the adherence in this present study was consistent with previous studies, even though our study had more patients included.

To our knowledge, only a few smaller studies have investigated the feasibility of LL-BFR in clinical settings for patients with

tendinopathies (Sata, 2005; Skovlund et al., 2020). A case series by Skovlund et al. investigated the feasibility of LL-BFR on patients with patellar tendinopathy (21). This study reported a 50% pain-reduction on NRS during a single-leg decline squat test, while the tendon vascularity was decreased by 31% after 3 weeks of low-load BFR resistance exercise (Skovlund et al., 2020). In line with these findings, a case report from 2005 observed reduced pain levels (without having reported the magnitude of this) and no thigh muscle atrophy after 3 weeks LL-BFR exercise in a patient showing patellar tendinitis (Sata, 2005). In both studies the adherence was comparable to the findings in the present study. Further, none of the studies reported any adverse events. However, both studies had few participants, and the exercise protocols consisted exclusively of supervised training sessions.

A concern regarding supervised exercise session in clinical populations is the limited flexibility in time, since both the patient and the supervisor has to have compatible timetables (Collado-Mateo et al., 2021). In this study, the supervised exercise sessions were performed at two sites to allow patients access to the supervised exercise session closer to either their home or worksite. Further, a session consisted of maximum four exercises (every second day from week 3) with no required exercise equipment beside the cuff, which was handed out at the hospitals at baseline. Additionally, in both the present study and the study by Mellor et al. patient education took place during the weekly, supervised sessions. This study design could enhance the patients understanding of their condition and expected benefit of the exercises (Collado-Mateo et al., 2021), resulting in a higher compliance to the protocol.

In the present study, one adverse event, leading to a drop out, was registered. There has been some discussion on the safety of LL-BFR, underreporting adverse events (Minniti et al., 2020) and the degree to which LL-BFR can cause serious muscle damage, such as exertional rhabdomyolysis (Wernbom et al., 2020). However, the patient reporting an adverse event in this study was not displaying symptoms related to rhabdomyolysis or other muscle damages, as the patient reported pain ease and continuation of daily exercise 2 weeks after the incident.

In general, LL-BFR seems to be a well-tolerated and a safe exercise modality in both healthy and clinical populations, when safety precautions concerning cuff application, cuff pressure, and time with blood flow restriction are taken (Hughes et al., 2017; Patterson et al., 2019).

Patient-Reported Outcomes

Improvements in patient reported outcomes shown in this study were comparable to Mellor et al. and Ganderton et al., although our patient population was slightly younger and had a longer period of pain duration before inclusion (Ganderton et al., 2018; Mellor et al., 2018). Changes in HAGOS score after an intervention in GT patients has to our knowledge, not been reported before. Five of the six subscales on HAGOS showed significant improvements. Additionally, a mean change within the minimal important change (MIC) of 10-15 points were seen in these five subscales (Thorborg et al., 2011). Even though the patients experienced less pain and better functioning, the subscale "participation in physical activities" (PA) only improved by 7 points. However, 14 patients had a duration of symptoms for at least 7 months suggesting that fear-avoidance or habits may have changed their approach to physical activities. Further, the PA subscale only consist of two items which make it a challenge to achieve a minimal important change.

Performance-Based Outcomes and Isometric Muscle Strength

In the present study, hip abduction strength measured at follow-up was comparable to the abduction strength in the exercising group in the study by Mellor et al. at 8 weeks follow-up (Mellor et al., 2018). Further, we found that mean hip extension peak torque increased for both legs and knee extension mean peak torque increased on the affected leg. Interestingly, the strength deficits observed at baseline between the affected and non-affected leg was minimized at follow-up. These gains in strength are reflected in the functional capacity tests, where the number of repetitions in the 30s-CST and the power output used in the SCT improved, indicating better function. Previous research by Fearon et al., suggested pain to be the main driver to activity limitation following GT (Fearon et al., 2017). Hence, the clinically relevant reduction in pain observed in the present study may have contributed to improvements in functional performance and muscle strength.

Adaptations Proximal to the Cuff

Intuitively, the muscular adaptations to LL-BFR are expected to occur distal to the cuff. Nevertheless, Hedt et al. focused a review on proximal muscle responses to BFR training and suggested a potential benefit of the tissue directly proximal to the occlusion site (Hedt et al., 2022).The mechanisms for proximal benefits of BFR requires more research. However, the authors suggested that increased muscle activation of the muscle proximal to the cuff due to downstream fatigue, mechanotransduction signaling (due to muscle cell swelling), metabolite signaling during release of cuff pressure, and systemic anabolic signaling (i.e. insulin growth factor-1, growth hormone) as potential mediators of the adaptations proximal to the occlusion site. Even though studies on proximal effects after BFR training primarily have focused on the upper extremity (Hedt et al., 2022), a RCT study by Bowman et al. has, in line with the present study, observed increased isometric hip abduction muscle strength following 6 weeks of unilateral LL-BFR training (Bowman et al., 2019).

LIMITATIONS

Some limitations to the present study must addressed. Given the lack of control group and a small sample-size, effect of the intervention, i.e., LL-BFR exercise and patient education, and the outcomes, cannot be evaluated in this study.

Furthermore, we chose to include women only, as GT mainly affects women, which may negatively affect the external validity. Moreover, we did not register how many patients were screened for eligibility to this study and have no overview of the overall patient flow in the three referring orthopaedic outpatient clinics, hence the included patients might not represent a broader population of patients with GT. Demographics of our population

is however, comparable to the women included in the studies by Grimaldi et al. (2017) and Mellor et al. (2018).

No imaging modalities were used to diagnose tendinopathy in the present study. However, the clinical tests used in this study, have been shown by Grimaldi et al. to be useful in diagnosing GT (Grimaldi et al., 2017).

A recent position stand by Patterson et al. (2019) proposed a guideline for applying LL-BFR training. Most of the recommendations are met in the present study in terms of cuff pressure and measurement of LOP, restriction time, rest time and frequency. However, the loading intensity and number of repetitions did not meet the guideline (Patterson et al., 2019), as Patterson et al. suggested using loading intensities of 20–40% of 1 repetition maximum (1RM) and a total of 75 repetitions. In the present study, exercises were performed with bodyweight only, thus, it is doubtful whether the proposed load has been met. Further, the maximal number of repetitions in an exercise reached 40 repetitions in 3 sets. The lower volume might be reflected in the patients perceived exertion-levels, as RPE was observed to be 2.25 (1.48). However, based on clinical experiences with patients suffering from GT and considering the proposed treatment strategies for controlling high tensile loads in patients with gluteal tendinopathy outlined by Grimaldi et al., an increased intensity of the exercises seems contraindicated (Grimaldi and Fearon, 2015). Thus, a low-load exercise protocol with slowly progression in exercise volume during the exercise period was considered viable. Another limitation related to the LL-BFR was the posture of which the patients had during the measurement of LOP. Hughes et al. have shown that LOP in the standing position is significantly higher than in a sitting position (Hughes et al., 2018). Since the patients in this study were sitting during the measurement of LOP for the mini-squats, the pressure in the cuff during the stand phase of the squat might have been lower than 60%.

CONCLUSION

The present study demonstrated that our exercise protocol using LL-BFR, and patient education was safe and feasible in female patients suffering from GT. Despite a low dropout, one adverse event occurred, which confirms the necessity for regular monitoring of patients engaging in LL-BFR. Nevertheless, patients reported a clinically relevant pain reduction, improved patient reported outcomes and increased physical performance. Additional research is highly needed in terms of determining effects of LL-BFR in GT. As proposed by Ganderton et al. (2018) and Mellor et al. (2018) the effectiveness of the patient education might be underrated. Hence, RCT studies addressing the impact of patient education alone, as well as LL-BFR alone on both functional and patient-reported outcomes in GT are warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NR, IM, MB, and SJ: contribution to conception. MB, SJ, and MH: design of the study. LT: performed the supervised exercise sessions at Aarhus University Hospital. MH: performed the supervised exercise sessions at Horsens Regional Hospital, handled the statistical analysis, and wrote the draft of the manuscript. All authors: reviewing and editing of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fspor.2022.881054/full#supplementary-material

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REVIEW
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Blood Flow Restriction Resistance Training in Tendon Rehabilitation: A Scoping Review on Intervention Parameters, Physiological Effects, and Outcomes

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Objective: To identify current evidence on blood flow restriction training (BFRT) in tendon injuries and healthy tendons, evaluating physiological tendon effects, intervention parameters, and outcomes.

Methods: This scoping review was reported in accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR). Databases searched included MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, Cochrane library (Controlled trials, Systematic reviews), and five trial registries. Two independent reviewers screened studies at title/abstract and full text. Following screening, data was extracted and charted, and presented as figures and tables alongside a narrative synthesis. Any study design conducted on adults, investigating the effects of BFRT on healthy tendons or tendon pathology were included. Data were extracted on physiological tendon effects, intervention parameters and outcomes with BFRT.

Results: Thirteen studies were included, three on tendinopathy, two on tendon ruptures, and eight on healthy Achilles, patellar, and supraspinatus tendons. A variety of outcomes were assessed, including pain, function, strength, and tendon morphological and mechanical properties, particularly changes in tendon thickness. BFRT intervention parameters were heterogeneously prescribed.

Conclusion: Despite a dearth of studies to date on the effects of BFRT on healthy tendons and in tendon pathologies, preliminary evidence for beneficial effects of BFRT on tendons and clinical outcomes is encouraging. As BFRT is a relatively novel method, definitive conclusions, and recommendations on BFRT in tendon rehabilitation cannot be made at present, which should be addressed in future research, due to the potential therapeutic benefits highlighted in this review.

Keywords: blood flow restriction, tendinopathy, resistance training, exercise, physiotherapy, tendon

INTRODUCTION

Tendinopathy is a disease entity which can cause significant pain and functional limitations for individuals and collectively places a tremendous burden on society through high healthcare costs (Hopkins et al., 2016; Dean et al., 2017). In chronic tendinopathy, tendons experience morphological changes and can present with increased tendon thickness, fibril disorganization, and neovascularization caused by repetitive tendon microtrauma (Magnusson and Kjaer, 2019; Millar et al., 2021). Tendinopathy prevalence has been shown to be higher in athletes due to frequent jumping, landing, running and change of direction movements (Zwerver et al., 2011). Collectively, tendinopathies can account for up to 30% of all musculoskeletal conditions requiring medical attention, with up to 22% of elite athletes having patellar tendinopathy at least once during their sporting careers (Lian et al., 2005; Skjong et al., 2012; Canosa-Carro et al., 2022). Complete and partial tendon ruptures are also common in both athletes and the general population with the Achilles tendon having the highest prevalence of ruptures (Nyyssonen et al., 2008). Like tendinopathy, tendon ruptures can also cause significant pain, disability and functional limitations and are associated with significant societal and healthcare costs, whether treated surgically or conservatively, with there being a lack of consensus on optimal treatment methods (Holm et al., 2015).

Resistance training has long been considered the treatment of choice in the rehabilitation of chronic tendinopathies, with both eccentric and heavy slow resistance training (HSRT) demonstrating positive clinical effects, for both improving symptoms and tendon structure (Kongsgaard et al., 2010; Beyer et al., 2015). Progressive resistance training is also considered an essential element of rehabilitation following tendon rupture to counteract muscle atrophy and stimulate tendon repair, whether treated conservatively or surgically (Christensen et al., 2020). The application of progressive tendon loads during rehabilitation is essential to not compromise tendon healing, with the precise dosage parameters of resistance training loading a critical consideration (Bohm et al., 2015). Prolonged time under tension with traditional heavy loads during the early phase of tendon rehabilitation could be counterproductive and compromise tendon healing (Loenneke et al., 2012a; Couppe et al., 2015). Blood flow restriction training (BFRT) is a method of resistance training which utilizes pneumatic cuffs or straps around a limb to partially restrict arterial blood flow, while simultaneously occluding venous outflow until the cessation of cuff pressure (Lorenz et al., 2021). BFRT also known as occlusion, hypoxic or Kaatsu training has become increasingly popular over the last decade as a method for enhancing strength gains in healthy populations such as athletes and more recently as a rehabilitation tool in those with musculoskeletal pathologies (Hughes et al., 2017; Barber-Westin and Noyes, 2019; Nitzsche et al., 2021). For example, BFRT has been found to be an efficacious method for increasing strength gains and muscle hypertrophy in rehabilitation following surgery for anterior cruciate ligament (ACL) rupture (Hughes et al., 2018; Caetano et al., 2021). The physiological benefits associated with BFRT, include beneficial adaptations to the cardiovascular, endocrine, and musculoskeletal systems with psychosocial benefits also reported such as mood and performance improvement (Karabulut et al., 2013, 2021; Neto et al., 2016; Silva et al., 2018; Bowman et al., 2019; da Silva et al., 2019; Okita et al., 2019; Freitas et al., 2021a; Miller et al., 2021).

Whilst traditional eccentric or HSRT for tendinopathy utilizes heavy training loads of up to 70% of 1 repetition maximum (1-RM), low-load BFRT (LL-BFRT) typically uses lower training intensities, and loads in the range of 20–40% of 1RM, which may be more tolerable for patients not able to tolerate high muscle-tendon training loads, while still preventing muscle atrophy and promoting hypertrophy (Centner et al., 2019a; Krzysztofik et al., 2019; Shiromaru et al., 2019; Kataoka et al., 2022). Interventional studies have found superior or similar clinical outcomes with LL-BFRT compared to conventional high-load resistance training (HL-RT) in knee rehabilitation for ACL reconstruction, patellofemoral pain, and knee osteoarthritis (Ohta et al., 2003; Bryk et al., 2016; Giles et al., 2017; Ferraz et al., 2018; Korakakis et al., 2018a; Ferlito et al., 2020; Grantham et al., 2021). BFRT has been shown to cause exercise-induced hypoalgesia through endogenous opioid and endocannabinoid mechanisms, so could therefore be a useful pain management tool in early musculoskeletal rehabilitation, particularly in the presence of an acute pain response (Korakakis et al., 2018b; Hughes and Patterson, 2019, 2020; Hughes et al., 2021). Recent evidence suggests that LL-BFRT may be a superior method for augmenting muscular adaptations in early musculoskeletal rehabilitation, which has been found to be comparably effective for inducing muscular hypertrophy and only minimally inferior for increasing muscular strength compared to HL-RT (Manini and Clark, 2009; Abe et al., 2012; Loenneke et al., 2012b; Yasuda et al., 2012; Martin-Hernandez et al., 2013; Lixandrao et al., 2018; Hughes et al., 2019a). The mechanisms of action of BFRT in muscular adaptation are thought to be related to increased inflammation and metabolic stress which can increase blood supply to muscles potentially stimulating muscle growth (Loenneke et al., 2012c; Pearson and Hussain, 2015; Rossi et al., 2018; Freitas et al., 2021a). Other speculated physiological mechanisms explaining muscle hypertrophy adaptations in response to BFRT includes activation of chemoreceptors, muscle swelling, and increased protein synthesis (Freitas et al., 2021a). Due to a paucity of research, it is unclear what effects BFRT may have on tendons, but the induced ischemic muscular milieu may facilitate morphological and mechanical tendon properties through enhanced collagen metabolism and tendon remodeling (Klein et al., 2001; Boesen et al., 2013). Despite these potential beneficial physiological mechanisms of BFRT on tendon healing, the method of training has received a dearth of attention in tendon rehabilitation, despite the clinical benefits found for other musculoskeletal conditions and the knowledge of resistance training being the most evidence-based treatment available for tendinopathies. Therefore, the objective of this scoping review is to evaluate current research on the use of BFRT for treating tendon injuries. The scoping review will be guided by addressing the following review questions on specific aspects of BFRT interventions within tendon rehabilitation: 1. What outcomes have been reported for BFRT in healthy tendons and

rehabilitation for tendon injuries and which outcome measures have been used? 2. What BFRT intervention and cuff parameters have been used in published studies? 3. What physiological mechanisms explaining effects of BFRT on tendons and tendon injuries have been investigated in published studies?

METHODS

Due to the exploratory nature of the research questions a scoping review was conducted as they are recommended for mapping key concepts, evidence gaps and types of evidence within a particular field and can help guide future research and the possibility of conducting systematic reviews on the topic (Tricco et al., 2018). The scoping review is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analysis extension for Scoping reviews known as the PRISMA-ScR (Tricco et al., 2018). This scoping review aimed to evaluate current BFRT interventions in healthy tendons and the rehabilitation of tendon injuries for the first time in the literature. The results will allow dissemination of the parameters of research BFRT interventions to clinical practitioners through peer-reviewed journal publication, allowing increased likelihood of implementation in clinical practice. The review will also outline future research and exercise reporting needs within BFRT interventions in tendon rehabilitation.

Eligibility Criteria

The inclusion criteria for the scoping review were guided by a modified PICO (PCoCo) as recommended for scoping reviews (Tricco et al., 2018). Studies including adults aged 18 years or older with a diagnosis of a tendon injury for any time duration were considered. Tendon injuries included both acute partial or full tendon tears or ruptures and any chronic tendon injuries diagnosed as any tendinopathy. Any tendon condition characterized by common tendinopathy symptoms, including full thickness tendon rupture were considered for inclusion. Studies including healthy participants with no history of tendon pathology were also included. Studies including participants with other concurrent injuries or medical conditions not tendon related were excluded. The concept of interest was BFRT for healthy tendons or for the treatment of any tendon related injury, including any type or format such as BFRT performed with bodyweight or external resistance. BFRT may be delivered across a range of settings by health or exercise professionals, delivered in a supervised or unsupervised manner, using any methods for training progression and monitoring. This scoping review considered both experimental and quasi-experimental study designs including randomized controlled trials and non-randomized controlled. In addition, prospective and retrospective cohort studies, case series and case reports were considered for inclusion. Unpublished studies, reviews or reports were not considered for inclusion.

Search Strategy

The search was carried out using a uniform search strategy across all databases (**Appendix 1**) and it included key words from two main concepts: Blood Flow Restriction ("Kaatsu," "Occlusion training"), and Tendon ("tendon," "tendinopathy," "tendon rupture"). The Boolean operators "Or" and "And" were used to link the key words from each concept and to link the concepts themselves, respectively. A 3-step search strategy was implemented in this scoping review. It incorporated the following: (1) a limited search of MEDLINE and CINAHL using initial keywords as, followed by analysis of the text words in the title/abstract and those used to describe articles to develop a full search strategy; (2) The full search strategy was adapted to each database and applied to MEDLINE, CINAHL, AMED, EMBase, SPORTDiscus, and the Cochrane library (Controlled trials, Systematic reviews). The following trial registries were also searched: ClinicalTrials.gov, ISRCTN, The Research Registry, EU-CTR (European Union Clinical Trials Registry), ANZCTR (Australia and New Zealand Clinical Trials Registry). Databases were searched from inception to March 1st, 2022 (Search performed on March 1st, 2022). The search for relevant gray literature included Open Gray, MedNar, Cochrane central register of controlled trials (CENTRAL), EThOS, CORE, and Google Scholar. (3) For each article located in steps 1 and 2, a search of cited and citing articles using Scopus and hand-searching where necessary, was conducted. Studies published in a language other than English were only considered if a translation was available as translation services are not available to the authors.

Study Selection

Following the search, all identified citations were collated and uploaded into RefWorks and duplicates removed. Titles and abstracts were then screened by two independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies were retrieved in full, and their citation details imported into Covidence (Veritas Health Innovation, Melbourne, Australia). Two independent reviewers assessed the full text of selected citations in detail against the inclusion criteria. Any disagreements that arose between the reviewers at each stage of the study selection process were resolved through discussion or by input from a third reviewer. The results of the search are reported in accordance with the PRISMA-ScR (Tricco et al., 2018). In accordance with guidance on conducting scoping reviews, critical appraisal was not conducted (Tricco et al., 2018).

Data Extraction

Data were extracted from sources included in the scoping review by one reviewer, with independent data extraction by a second reviewer for at least 10% of studies. The data extracted included specific details regarding the population, concept, context, study methods and key findings relevant to the review questions. The data extracted included dimensions such as study type, purpose, population and sample size, methods, details of the BFRT intervention, specific exercises and outcome measures used. Details of the BFRT interventions included type, dosage, cuff parameters, and methods used to progress and adjust the training stimulus. Data were also be extracted on any physiological mechanisms which have been investigated to explain the effects of BFRT on tendons, and positive clinical outcomes. Decreased

muscle size and strength are associated with tendon injuries, both for risk and a consequence of pathology. Therefore, data on muscle strength and size outcomes will also be extracted as improvements in muscle size and strength would be positive clinical outcomes in tendon rehabilitation, although not directly related to physiological tendon changes. The extracted data are presented in **Table 1** with a narrative synthesis accompanying the tabulated results.

RESULTS

Included Study Characteristics

The literature search yielded 29 articles, of which 13 met the inclusion criteria and were included in the review, which is summarized in the PRISMA flow chart (**Figure 1**), with an overview of the characteristics and outcomes of the included studies provided in **Table 1**. Five studies investigated the effects of BFRT on tendon pathologies, three on patellar tendinopathy, including one case series (Skovlund et al., 2020) and two case reports (Sata, 2005; Cuddeford and Brumitt, 2020). Two case reports investigated BFRT with tendon ruptures, one on biceps tendon rupture (Wentzell, 2018) and one on Achilles tendon rupture (Yow et al., 2018). Eight studies investigated the effects of BFRT on healthy tendons, five on the Achilles tendon, including four RCTs (Centner et al., 2019b; Chulvi-Medrano et al., 2020; Gavanda et al., 2020; Picon-Martinez et al., 2021) and one cross-sectional study (Canfer et al., 2021), one RCT on the patellar tendon (Centner et al., 2021), one RCT on the supraspinatus tendon (Brumitt et al., 2020), and one cohort study on the patellar tendon (Kubo et al., 2006). The sample sizes of included studies ranged from 1 to 56, with only 12 participants in total for tendon pathologies out of a total of 292 participants, with most included participants having healthy tendons. All included studies investigated the effects of a LL-BFRT intervention, five in isolation (Sata, 2005; Wentzell, 2018; Yow et al., 2018; Cuddeford and Brumitt, 2020; Skovlund et al., 2020) four compared with LL-RT (Brumitt et al., 2020; Chulvi-Medrano et al., 2020; Gavanda et al., 2020; Canfer et al., 2021), three compared with HL-RT (Kubo et al., 2006; Centner et al., 2019b, 2021), and one with both LL-RT and HL-RT (Picon-Martinez et al., 2021). The duration of BFRT interventions ranged from a single session to 14 weeks. The most common exercises used for the BFRT interventions were, plantarflexion calf raises (8), leg press (4), and knee extension (2).

Outcome Measures

Four studies assessed pain as an outcome measure with BFRT, two with VAS scales and two with NRS-P scales. Patient reported function scales were assessed in three studies, with two using the Victorian Institute of Sport Assessment Patellar (VISA-P) for patellar tendinopathy and one using both the Disabilities of the Arm, Shoulder, and Hand (DASH) and Mayo Elbow Performance Index score for biceps tendon rupture. Seven studies assessed strength as an outcome, with five using dynamometry, one using 1-RM testing and one using an isokinetic Biodex system. Eight studies used ultrasound (US) to assess tendon mechanical and morphological properties, with tendon thickness the most assessed tendon outcome, measured in five studies, with four studies also assessing tendon stiffness. Muscle properties were assessed in four studies, with three studies using US to assess muscle volume or cross-sectional area and one using magnetic resonance imaging (MRI). One study used thermograms to assess Achilles tendon skin temperature. One study assessed power using an isokinetic Biodex system. One study used MRI to assess tendon signal intensity (echogenicity).

Outcomes

The five studies that investigated the effects of a BFRT intervention on a tendon pathology, all found clinical improvements in pain, function, and muscle strength for included patients, with athletic patients being able to return to sport. The eight studies that investigated BFRT on populations with healthy tendons, all found beneficial physiological effects on tendon morphology and mechanical properties, including beneficial changes in tendon stiffness, thickness, vascularity, signal intensity, and skin temperature. However, two studies did not find changes in tendon stiffness following BFRT. Several studies also found increases in muscle volume and cross-sectional area which was associated with increases in muscular strength and decreased pain levels.

Training Parameters

All included studies applied a BFRT cuff to either the proximal or distal limb of the targeted joint, however there were wide variances in the type and size of cuffs used, with cuff width ranging from 7 to 15 cm. Occlusion pressure was calculated as either absolute pressure ranging from 80 to 180 mm Hg, or a percentage of arterial occlusion ranging from 30 to 80%. There were wide variances in the sets and repetitions of prescribed exercises, with the commonly recommended BFRT protocol of four sets of 30, 15, 15, and 15 repetitions being implemented in seven studies. The number of sets across studies ranged from 3-6, with repetitions ranging from 5 to 30, with one study using muscular failure instead of predefined repetitions. Training frequency ranged from 2 to 7 times per week, with training intensity most commonly at 30% of 1-RM, as applied in nine studies. Most studies did not report how the training stimulus was progressed, with two studies progressively increasing occlusion pressure, one increasing percentage of 1-RM (20–35%), and two studies reported using small increases in external weight. Rest time between exercises was 30 s in seven studies and 1 min in two studies, with four studies reporting 3 min rest between different exercises, with three of these studies deflating cuff pressure between exercises.

DISCUSSION

The main findings of this scoping review were that despite the dearth of studies available on the effects of BFRT on tendons, studies do indicate that BFRT can produce beneficial effects on tendons. Preliminary evidence from case series and case reports indicates that BFRT may be helpful for improving clinical outcomes such as pain in function in rehabilitation of tendinopathy and tendon ruptures, however no RCTs have been conducted in these populations. The evidence for beneficial

TABLE 1 | Characterizes of included studies and BFRT intervention parameters.

Author, Study design, population	Intervention, exercises, duration	Training parameters	Cuff parameters	Outcome measures	Outcomes, results
Skovlund et al. (2020) Case series, $n = 7$, Patellar tendinopathy	Low-load BFRT: SL leg press, knee extension, 3 weeks	Sets: 6, Reps: 5–30, Freq: 3 × WK, Prog: increase volume based on pain response, Int: 10RM, (30% of 1RM). Maximum 105 reps per session	Polyester cuff (15 cm wide) fitted at proximal thigh. Occlusion pressure: 120 mm Hg Cuff pressure released for 3 Min between exercises.	Pain (NRS-P, SLDS), Function (VISA-P) Tendon vascularity (US), Knee extensor strength (MVC – static dynamometry)	Intervention was effective for improving clinical outcomes. Pain with SLDS reduced by 50%. Tendon vascularity diminished by 31% following 3 weeks. No changes in tendon thickness. Increase in knee extensor strength. Adherence: 98%
Cuddeford and Brumitt (2020) Case report, $n = 1$, Patellar tendinopathy	Low-load BFRT: SL leg press, SLDS, 12 weeks	Sets:4, Reps 15–30; Freq 2 × WK: Prog: increase resistance (10lbs Inc), Int: 15-30RM (1RM testing)	Delfi tourniquet system fitted at proximal lower extremity. Occlusion pressure: 80% restriction of arterial inflow. 30 second rest between sets (cuff not removed)	Pain (VAS), Function (VISA-P), Tendon size US, Hip and knee strength (handheld dynamometry, SL leg press 1RM)	Patients improved clinical outcomes and returned to sports activity. Improvements in tendon thickness and resolution of hypoechoic region. Increased lower limb strength Adherence: supervised.
Sata (2005), Case report, $n = 1$, Patellar tendinopathy	Low-load BFRT: straight leg raises, hip abduction and adduction, calf raise, toe raise, squat, crunch, back extension, basketball shooting, 3 weeks	Sets: 3, Reps; 15, Freq: 5-6 × WK, Prog: Int:15rm (30% of 1RM)	Kaatsu cuff fitted at proximal lower limb. Occlusion pressure range: 160–180 mmHg.	MRI (signal intensity). Thigh circumference	Patient improved clinical outcomes and returned to playing basketball. MRI signal intensity was reduced, and the thigh circumference was increased by 7 mm and 2 mm for the right and left sides. Adherence: NR
Wentzell (2018), Case report, $n = 1$, Biceps tendon rupture	Manual therapy, laser therapy, progressive strength training including Low-load BFRT: Isometric forearm pronation & supination, elbow flexion & extension 14 weeks	Sets: 4, Reps: 30,15,15,15, Freq: 7 × WK, Prog: increase resistance (1.5-4lbs) difficulty and ROM, Int: 10-30% MVC	Blood pressure cuff fitted at proximal arm. Occlusion pressure: 80 mmHg.	Pain (NPRS), Function DASH, Mayo Elbow Performance Index score.	Patient improved clinical outcomes and returned to preinjury activity (weightlifter). Adherence: NR
Yow et al. (2018) Case report, $n = 2$, Achilles tendon rupture	Low-load BFRT: Leg press, calf press, 6 weeks	Sets: 4, Reps: 30,15,15,15, Freq: NR, Prog: NR, Int: 30% of 1RM	Delfi tourniquet system (14 cm wide) fitted at proximal thigh. Occlusion pressure: 80%, 180 mm Hg.	Strength and power (isokinetic testing—Biodex system).	Patients improved strength and power and returned to sports. Adherence: NR
Centner et al. (2019b) RCT, $n = 55$, Healthy Achilles tendon	1. Low-load BFRT: standing and seated calf raises (20-35% 1RM). 2. High load RT (70-85% 1RM). 3. Non-exercise control, 14 weeks	Sets:3, Reps;6-12, Freq: 3 × WK, Prog: increase resistance (5% of 1rm every 4 WK, 20–35%), Int: 20–35% of 1RM Rest: 1 MIN between sets, 3 MIN between exercises	Pneumatic nylon tourniquet (12 cm wide) fitted on proximal thigh. Occlusion pressure: 50% arterial occlusion. Pressure maintained during 1 MIN rest; cuff deflated during 3 MIN rest.	Tendon morphology, Mechanical and material properties (US), and muscle (US) cross-sectional area (CSA) and isometric strength (MVC—isokinetic dynamometer).	Both groups induced significant increases in tendon stiffness and CSA, which were comparable between groups. Gastrocnemius CSA and plantar flexor strength significantly increased in both groups. No changes in control group. Adherence: supervised
Centner et al. (2021) RCT, $N = 29$, Healthy patellar tendon	1. Low-load BFRT: bilateral leg press and knee extension, standing and seated calf raises (20–35% 1RM) 2. High load RT (70–85% 1RM), 14 weeks	Sets: 4, Reps: 30,15,15,15, Freq: 3 × WK, Prog: increase resistance (5% of 1rm every 4 WK, 20–35%), Int: 20–35% of 1RM Rest: 1 MIN between sets, 3 MIN between exercises	Pneumatic nylon tourniquet (12 cm wide) fitted on proximal thigh. Occlusion pressure: 50% arterial occlusion. Pressure maintained during 1 MIN rest; cuff deflated during 3 MIN rest.	Tendon morphology, mechanical and material properties (US and MRI), and muscle (MRI) cross-sectional area (CSA) and strength (dynamic 1RM).	Both groups induced significant increases in tendon stiffness and CSA, muscle mass and strength, which were comparable and not significantly different between groups. Knee extension 1RM was higher in BFRT group. Adherence: supervised

(Continued)

TABLE 1 | Continued

Author, Study design, population	Intervention, exercises, duration	Training parameters	Cuff parameters	Outcome measures	Outcomes, results
Chulvi-Medrano et al. (2020) RCT, $n = 56$, Healthy Achilles tendon	1. LL BFRT: plantarflexion 2. LL RT, single session	Sets:3, Reps; 15, Freq: single session, Prog: NR, Int: 30% of 1RM Rest: 30 s between sets	High precision compression meter (57 cm long × 9 cm wide) fitted on proximal thigh. Occlusion pressure: 30%.	Tendon thickness (US)	BFRT group had significantly greater decrease in tendon thickness compared to LL-RT, immediately and 24 h after exercise, which may be associated with neurotendinous fluid movement in response to BFRT. Adherence: NR
Gavanda et al. (2020) RCT, $n = 21$, Healthy achilles tendon	1. LL BFRT: plantarflexion 2. LL RT, 6 weeks	Sets:4, Reps; to muscular failure, Freq: 2 × WK, Prog: occlusion pressure increased every 4 WKs, Int: 30% of 1RM, Rest: 30 s between sets	Twist lock (7 cm wide) cuffs fitted below patella. Occlusion pressure: 60%.	Calf volume and muscle thickness (US), maximal hopping test for leg stiffness, 1-RM smith machine calf raise, pain (VAS)	Leg stiffness and calf volume did not change. VAS, 1RM, and muscle thickness improved equally in both groups. No difference found in leg stiffness between groups: used to measure tendon adaptations. Adherence: NR
Kubo et al. (2006), Cohort, $n = 9$, Healthy patellar tendon	1. LL BFRT (20% of 1RM): plantarflexion 2. HL RT (80% of 1RM), 12 weeks	Sets:4, Reps; 25, 18, 15, 12, Freq: 3 × WK, Prog: NR, Int: 20% of 1RM Rest: 30 s between sets	Elastic pneumatic belt fitted on proximal thigh. Occlusion pressure: 37.7%.	Knee extension MVC (dynamometer) and muscle volume. Specific tension of vastus lateralis (VL), Tendon stiffness (US)	Both groups significantly increased MVC and muscle volume of quadriceps. Tension of VL increased significantly 5.5% for HL, but not for LL. Tension and tendon properties were found to remain following LL-BFRT, whereas they increased significantly after HL-RT. BFRT did not alter tendon stiffness, while the HL protocol increased it significantly. Adherence: NR
Picon-martinez et al. (2021) RCT, $n = 52$, healthy achilles tendon	1. LL BFRT (30% 1RM): plantarflexion 2. LL RT (30% 1RM) 3. HL RT (75% 1RM), single session	Sets:4, Reps; 30, 15, 15, 15, Freq: single session, Prog NR, Int: 30% of 1RM, Rest: 30 s between sets	Pneumatic CUFF (9 cm width) fitted under knee joint. Occlusion pressure: 30%.	Achilles tendon thickness (US): immediately, 60MIN and 24 h after training.	Achilles tendon thickness was significantly reduced immediately after, 60 min and 24 h post-LL BFRT group and remained unchanged in the other groups. Adherence: NR
Brumitt et al. (2020) RCT, $n = 46$, healthy supraspinatus tendon	1. LL BFRT: side-lying external rotation 2. LL RT, 8 weeks	Sets:4, Reps; 30, 15, 15, 15, Freq: 2 × WK, Prog: NR, Int: 30% of 1RM Rest: 30 s between sets	Delfi tourniquet system fitted at proximal upper arm. Occlusion pressure: 50%,	Rotator cuff strength (dynamometry), supraspinatus tendon thickness (US)	BFRT did not augment rotator cuff strength gains or tendon thickness when compared to RT. Both groups significantly increased rotator cuff strength and supraspinatus tendon thickness, with no significant difference between groups. Adherence: supervised
Canfer et al. (2021) cross sectional, $n = 12$, healthy achilles tendon	1. LL BFRT: bodyweight SL heel raise 2. LL RT	Sets:4, Reps; 30, 15, 15, 15, Freq: single session, Prog: NR, Int: 30% of 1RM Rest: 30 s between sets	Occlusion cuff (7 cm) fitted at distal lower leg. Occlusion pressure: 80%. Cuff only deflated after 4th set.	Thermograms to assess Achilles tendon skin temperature (Tskin)	A lower Tskin was seen following BFRT exercise at the tendon insertion, but not at the free tendon or the musculotendinous junction. A significant effect of time upon changes in Tskin were observed in both groups. Adherence: NR

LL-BFRT, low-load blood flow restriction training; HL-RT, high load resistance training; RM, repetition maximum; Tskin, skin temperature; SL, single leg; US, ultrasound; MRI, magnetic resonance imaging; MIN, minute; NR, not reported; Int, intensity; Freq, frequency; Prog, Progression; RCT, randomized controlled trial; VL, vastus lateralis; MVC, maximum voluntary contraction; VAS, visual anologue scale; NRS-P, pain numeric rating scale; VISA-P, Victorian Institute of Sport Assessment Patellar; SLDS, single leg decline squat; n, number; WK, week; ROM, range of motion.

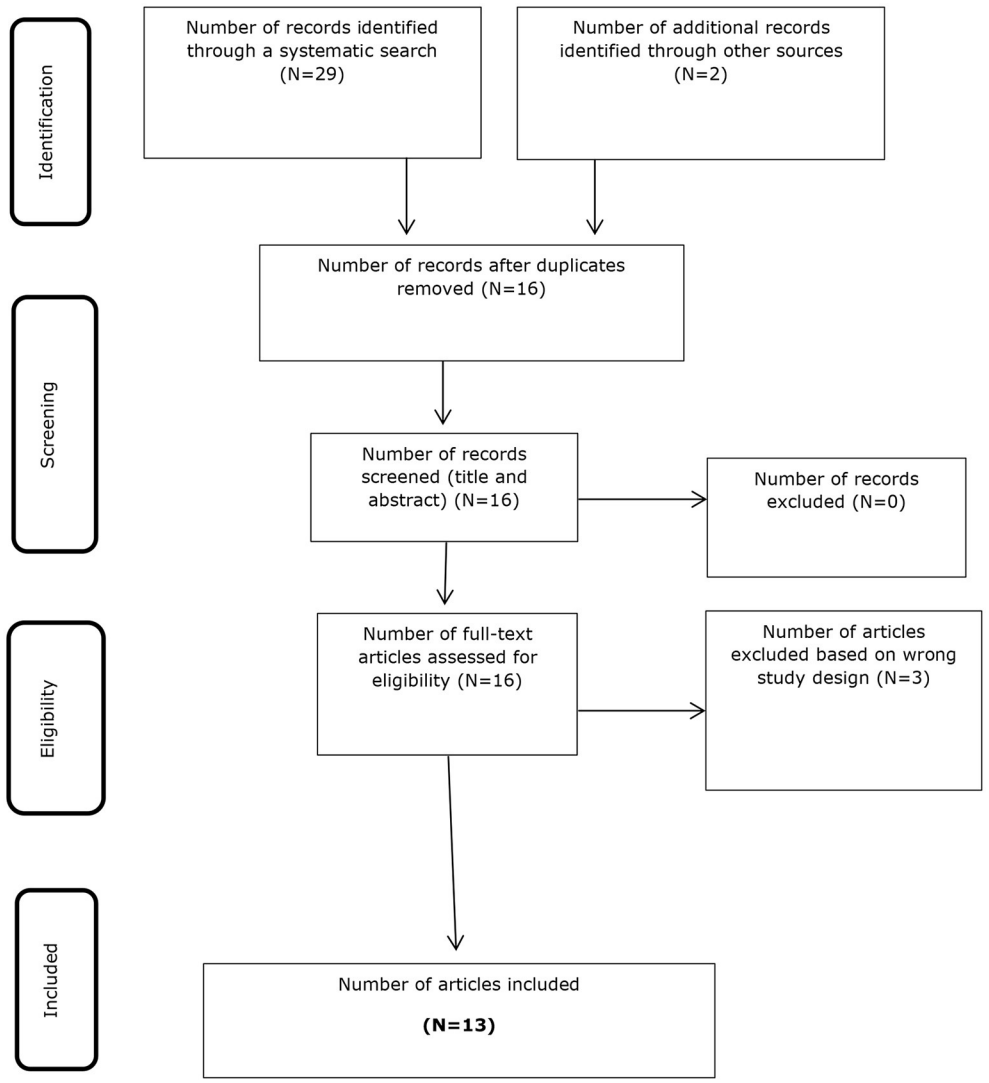

FIGURE 1 | PRISMA study flow diagram.

changes in healthy tendons is more robust due to several RCTs on the topic, showing beneficial physiological effects on tendon morphology and mechanical properties, including increases in tendon stiffness, with reductions in tendon thickness, vascularity, signal intensity (echogenicity) and skin temperature. Although it is unclear if these beneficial effects found in healthy tendons would also occur with pathological tendons, the preliminary evidence suggesting clinical improvement with BFRT in tendon pathology, is suggestive of potential comparable physiological benefits in tendon pathology. There is a clear need for further interventional studies of BFRT in tendinopathy and tendon rupture rehabilitation, with high quality large scale RCTs required to reach definitive conclusions and recommendations for BFRT in tendon pathology. However, there is a clear scientific rationale for the potential of clinical improvements in tendon pathology with BFRT as evidenced by the beneficial effects seen in healthy tendons, and the improvement of clinical outcomes with BFRT in other musculoskeletal disorders (Ohta et al., 2003; Bryk et al., 2016; Giles et al., 2017; Ferraz et al., 2018; Korakakis et al., 2018a; Ferlito et al., 2020; Grantham et al., 2021). Given the increased research interest and clinical use of BFRT in musculoskeletal rehabilitation for non-tendon pathologies, the dearth of available studies applying BFRT to tendon pathologies could be considered somewhat surprising. This is particularly relevant considering resistance training is considered the gold-standard first-line treatment intervention for tendinopathies, particularly Achilles and patellar tendinopathy, due to a plethora of evidence showing the clinical efficacy of resistance training such as eccentric and heavy slow resistance training (Burton and McCormack, 2021). Perhaps the belief that resistance training in tendinopathy must include high training loads has been a limiting factor in the application of

LL-BFRT and could explain why it is an underutilized tool in tendon rehabilitation.

The evidence from RCTs comparing LL-BFRT with HL-RT, suggests comparable outcomes for improving muscle and tendon properties (Centner et al., 2019b, 2021), with these changes possibly serving as the mechanisms to explain the clinical benefit seen with BFRT in the case reports in tendinopathy and tendon rupture rehabilitation. The first RCT investigating the effects of LL-BFRT compared to HL-RT in patellar tendinopathy has been registered in Denmark, by the authors who conducted the positive case series included in this review (Skovlund et al., 2020). This trial will be the first step in determining if a shift is required in the tendinopathy rehabilitation field, from the belief that HL-RT is a prerequisite for improving outcomes in tendinopathy, to a possible future where both HL-RT and LL-BFRT are both viable rehabilitation methods, giving clinicians and patients more options and choice during rehabilitation. This may be particularly relevant for non-athletic patients who are unaccustomed to training with heavy loads, sedentary elderly patients, or those who may have contraindications to heavy training and those with an acute painful or reactive tendinopathy or recent tendon rupture, who would be unable to tolerate the loads required with HL-RT. In the rehabilitation of ACL ruptures, LL-BFRT has been found to be a beneficial training method for increasing muscular adaptations in those who have difficultly performing HL-RT (Palmieri-Smith and Lepley, 2015). Furthermore, LL-BFRT has been shown to attenuate pain, increase strength and improve function in rehabilitation for hospital inpatients (Ladlow et al., 2018), ACL rupture (Patterson et al., 2019), patellofemoral pain (Constantinou et al., 2022), rheumatoid arthritis (Rodrigues et al., 2020), ankle fractures (Larsen et al., 2021), and knee osteoarthritis (Ferraz et al., 2018), suggesting pain improvement may be possible with lower training loads in tendon injuries without requiring all patients to undertake HL-RT.

Included studies used low training intensities, with most programming training based on a percentage of an individual's 1-RM, typically 30%, which is congruent with loads between 20 and 40% of 1RM which are typically recommended in the BFRT literature (Kilgas et al., 2019). It is well-established that LL-BFRT requires a higher volume of repetitions to derive physiological adaptations (Kraemer and Ratamess, 2004), with the 30-15-15-15 program of 75 repetitions per set, completed with four sets typically recommended (Patterson et al., 2019). Whilst seven studies implemented this regime, the number of sets across studies ranged from 3 to 6, with repetitions ranging from 5 to 30, with one study using muscular failure instead of predefined repetitions. It is unclear if training to volitional muscular failure with BFRT is required to derive adaptations, with previous BFRT studies suggesting it may be unnecessary (Patterson et al., 2019). Previous studies have shown that muscular failure is not required for muscle hypertrophy, with overall training load volume considered more relevant for augmenting hypertrophy (Schoenfeld et al., 2017, 2019; Lasevicius et al., 2018, 2019). Details on rest periods and whether cuff pressure was maintained or deflated between sets and exercises varied across studies. However, previous research has shown that rest with an inflated or deflated cuff are viable options (Yasuda et al., 2013), although longer rest periods may reduce metabolic stress and therefore limit potential adaptations compared to short rest periods (Loenneke et al., 2010a,b; Patterson et al., 2019). Despite large variances in the BFRT arterial occlusion pressure of included studies which ranged from 30 to 80%, recommendations for occlusion pressure in the literature do range from 40 to 80% (Loenneke et al., 2011; Patterson et al., 2019), suggesting pressure should be individualized based on measures of arterial pressure and comfort levels (Jessee et al., 2016; Mattocks et al., 2017).

This review has several limitations, particularly the small number of studies included, with only five studies on tendon pathology, all being case series or case reports, highlighting the need for future high-quality studies with larger sample sizes, as there are no RCTs on BFRT in tendon pathology currently available. Future studies should also investigate the effects on specific subgroups known to be at increased risk for tendon injuries such as athletes. There was considerable heterogeneity of the BFRT parameters implemented in studies, with standardized methods and reporting of interventions required in future BFRT studies in tendon rehabilitation to enhance clinical translation of the research interventions. The longest follow-up times of included BFRT interventions were 14 weeks, with much longer follow up times required to assess the long-term adaptations and outcomes of BFRT on healthy and pathological tendons. Methods for monitoring and recording adherence to BFRT should also be emphasized in future studies as several included studies did not report the adherence level to BFRT, which may vary due to perceptual responses and comfort which may affect reported clinical outcomes (Loenneke et al., 2011; Martin-Hernandez et al., 2017; Freitas et al., 2021b; Suga et al., 2021).

PERSPECTIVES

The superiority of LL-BFRT over standard LL-RT for muscular adaptations have been previously highlighted (Takarada et al., 2002; Madarame et al., 2008; Abe et al., 2010a,b; Yasuda et al., 2010; Centner et al., 2019c; Lambert et al., 2021), with findings from this review suggesting the same may be true for tendon adaptations. However, it remains unclear whether LL-BFRT or standard HL-RT is a superior method for inducing muscular adaptations, with some studies finding equal benefit for muscle strength gains (Lixandrao et al., 2015; Vechin et al., 2015; Curran et al., 2020; Gronfeldt et al., 2020; Hill et al., 2020) and others suggesting HL-RT is a superior method (Hughes et al., 2019b). Some studies included in this review suggest that the tendon adaptations in the healthy Achilles and patellar tendon following LL-BFRT are comparable to those evoked by HL-RT, which is an encouraging finding for the field of tendon rehabilitation (Centner et al., 2019b, 2021). However, these comparable beneficial tendon adaptations found in the high-quality RCTs on healthy tendons need to be investigated in high-quality RCTs in tendon pathology before conclusions can be drawn and recommendations made. Such findings, if found to be comparable and translate in tendon pathology may require a paradigm shift in the

tendinopathy rehabilitation field in relation to the prescription of resistance training interventions, particularly for select populations not able to tolerate the standard and proven HL-RT interventions (Loenneke et al., 2013).

CONCLUSION

Despite a dearth of studies to date on the effects of BFRT on healthy tendons and in tendon pathologies such as tendinopathy, preliminary evidence for beneficial effects of BFRT on tendons and clinical outcomes is encouraging. As BFRT is a relatively novel method, particularly its application in musculoskeletal rehabilitation, definitive conclusions, and recommendations on BFRT in tendon rehabilitation cannot be made at present, which should be addressed in future research, due to the potential therapeutic benefits highlighted in this review. The addition of LL-BFRT as a viable rehabilitation method in tendinopathy rehabilitation would be complimentary to currently utilized HL-RT interventions and provide more rehabilitation options for patients unable to tolerate HL-RT during tendon rehabilitation.

AUTHOR CONTRIBUTIONS

IB conceptualized the work, developed the methods, search strategy, and framework for the review. IB and AM contributed to the development of the research questions and the study design. Both authors developed the first and subsequent drafts of the manuscript and reviewed and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fspor.2022.879860/full#supplementary-material

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Impact of a Six-Week Prehabilitation With Blood-Flow Restriction Training on Pre- and Postoperative Skeletal Muscle Mass and Strength in Patients Receiving Primary Total Knee Arthroplasty

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Introduction: Total Knee Arthroplasty (TKA) is one of the most successful interventions in gonarthrosis, however the operation is leading to muscle atrophy and long-term muscular deficits. To enhance rehabilitation after TKA, exercise programs try to improve muscle function preoperatively, called prehabilitation. Blood-Flow-Restriction Exercises (BFRE) is a training method which is characterized by using tourniquets to reduce arterial and occlude venous blood flow simultaneously during the exercise to increase metabolic stress. The present study aimed to evaluate the effects of a 6-week prehabilitation with BFR on pre- and postoperative muscle mass, strength, and quality of life (QoL).

Methods: 30 patients with end-stage gonarthrosis participated in this study. Patients were randomized into one of three groups: 1) Control-Group (CON): Standard clinical approach without prehabilitation. 2) Active-Control-Group (AC): Participation in a prehabilitation with sham-BFR. 3) BFR-Group (BFR): Participation in a prehabilitation with BFR. The prehabilitation protocol consist of a cycling-ergometer-based training performed twice per week over 6 weeks. During exercise, BFR was applied periodically three times per leg with a pressure of 40% of the individual-limb-occlusion-pressure. Measurement time points were six- (baseline), 3-weeks and 5-days before the surgery (Pre-OP), as well as three- and 6-months postoperatively. Outcome measures were muscular strength of the thigh muscles, thigh circumference as well as QoL and functional activity, examined by 6-min walking- and chair rising test.

Results: Both training groups indicated significantly improved leg muscle strength following the prehabilitation period with a superior effect for the BFR-group (BFR: ~170% vs. AC: ~91%, $p < 0.05$). No significant changes in leg strength occurred in the CON (~3%, $p = 0.100$). Further, patients in BFR-group indicated significantly improved

skeletal muscle mass assessed by femoral circumference following prehabilitation period (~7%, $p < 0.05$), while no significant changes occurred in the CON (–1.14%, $p = 0.131$) and AC-group (~3%, $p = 0.078$). At 3-months Post-OP, the CON and BFR-group revealed a significant decrease in femoral circumference compared to the Pre-OP (CON: ~3%, BFR: ~4%; $p < 0.05$), but BFR-group remained above the baseline level (~3%, $p < 0.05$). No significant change in femoral circumference was found for AC-group (~2%, $p = 0.078$). In addition, the prehabilitation with BFR provided notably improved Knee Injury and Osteoarthritis Outcome Scores (KOOS) especially in pain perception with significant higher effect compared to other groups (CON: –2%, AC: 13%, BFR: 41%; $p < 0.05$). In long-term rehabilitation after 6-months, all groups showed significantly improved KOOS scores in all dimensions (CON: ~110%, AC: ~132%, BFR: ~225%; $p < 0.01$), and functional examinations (CON: ~26%, AC: ~16%, BFR: ~53%; $p < 0.01$).

Conclusion: The present findings show that BFR-prehabilitation induce significant improvements in muscle function and QoL before TKA surgery. In addition, the supporting effect of prehabilitation on postoperative regeneration and QoL should be highlighted, illustrating prolonged beneficial effects of BFR on muscular and functional performance in a "better in, better out"-manner.

Keywords: venous occlusion, kaatsu training, muscle atrophy, rehabilitation, exercise therapy

INTRODUCTION

Total Knee Arthroplasty (TKA) is one of the most popular and successful interventions in gonarthrosis leading to significant improvements in subjective pain and quality of life (QoL) (Vos et al., 2012). However, knee osteoarthritis (OA) as well as surgical therapy have adverse effects on skeletal muscle mass and strength (Franz et al., 2019). Predominantly due to pain-related reductions in mobility and exercise, patients receiving TKA are characterized by reduced muscular function preoperatively (Dreyer et al., 2013). Although postoperative rehabilitation shows a significant impact on patient mobility and QoL, recent meta-analyses show that TKA patients are affected by persistent muscle weakness and atrophy for several years (LaStayo et al., 2009; Thomas and Stevens-Lapsley, 2012).

Since physical patient characteristics like muscle mass, strength and functionality can be seen as positive predicate outcomes parameters for a successful rehabilitation (Mizner RL. et al., 2005; Devasenapathy et al., 2019), several studies try to support rehabilitation after TKA by improving muscle function already preoperatively through exercise, called prehabilitation. Unfortunately, common training techniques cannot provide an adequate stimulus for muscular adaptations without provoking increased pain (Juhl et al., 2014). Consequently, the current impact of available prehabilitation concepts is rated as only slight to moderate (Wang et al., 2016; Moyer et al., 2017).

Blood-Flow-Restriction Exercises (BFRE) are a new training method that is characterized by the use of specialized tourniquets to restrict venous and reduce arterial blood flow during the exercise in the working limb to increase metabolic stress. Since BFRE can gain significant effects on muscle mass and strength by using only low mechanical loads (Ferraz et al., 2018; Franz et al., 2020) its application in patients with degenerative joint diseases could be able to improve the applicability and effectiveness of prehabilitation concepts (Franz et al., 2018; Žargi et al., 2018; Kacin et al., 2021).

Therefore, the present study aimed to assess the impact of a 6-week prehabilitation protocol with BFRE on pre- and postoperative muscle mass, strength, functionality and subjective pain perception in patients receiving an elective primary TKA.

METHODS

Subjects

30 patients suffering from end-stage gonarthrosis (male = 18, female = 12, age = 63.5 ± 8.1 y, height = 176.4 ± 7.2 cm, weight = 86.9 ± 16.1 kg) participated in this study. Patients were randomly assigned into one of three groups: 1) Control-Group (CON): This group followed the standard clinical treatment without a specialized prehabilitation protocol. 2) Active-Control-Group (AC): The second group followed the standard clinical treatment and participated in a 6-week prehabilitation protocol with a sham-BFR application. 3) BFR-Group (BFR): The third group followed the standard clinical treatment and participated in a 6-week prehabilitation protocol with additional BFR application. The standard clinical treatment consists of the surgery and 7 days of hospitalization with daily physical therapy, which was followed by 3 weeks of inpatient rehabilitation.

Study Design

The study design consists of a prospective, single blinded, parallel study design to determine the influence of

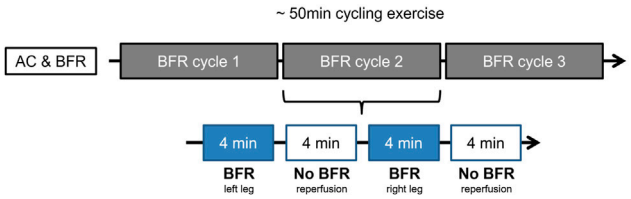

FIGURE 1 | Example of prehabilitation week four for AC- and BFR-group. The 50-min ergometer exercise is divided into three cycles. Each cycle consists of the application of the BFR stimulus to both legs in alternation, followed by a rest. As shown here, the left leg is loaded with BFR first (for 4 minutes in week four), followed by a rest of 4 min. This is followed by BFR application to the right leg with a subsequent break. This cycle is repeated a total of three times.

prehabilitation on pre- and postoperative skeletal muscle mass and strength. While the CON underwent routine clinical practice without prehabilitation, the other groups completed an identical 6-week prehabilitation protocol, one with additional BFRE (BFR-Group) and one with a sham-BFR application (AC-Group) before TKA, to reduce a potential bias in expectations of the intervention effect between groups. Preliminary visits were conducted before the start of the study to familiarize the patients with the cycling ergometer, testing protocols and tourniquet pressures.

Measurement time points were 6 weeks- (baseline), 3 weeks- (3w-Prehab) and 5 days before surgery (Pre-OP), as well as 3- (3m-Post-OP) and 6-months (6m-Post-OP) postoperatively.

Prehabilitation

The prehabilitation protocol consist of a cycling ergometer-based training protocol performed twice per week for about 50 min with an individualized intensity. Ergometer intensity was determined based on a calculated exercise heart rate (EHR) (Mangione et al., 1999).

For determination of EHR, maximal heart rate [HR (max) = 220—Age) and heart rate reserve (HRR = HR (max)—HR (rest)] of each participant was calculated. Subsequently, the EHR was determined by the following calculation model:

$$EHR = HR(rest) + (HRR\,x\,0.5)$$

The load in watts matching the calculated EHR was determined during an incremental step test on the cycling ergometer. The test person starts at an intensity of 20 W (W) on the cycling ergometer, which was increased by 20 W every 3 minutes. Vital signs such as blood pressure (RR) and HR are determined at the beginning and end of each stage. As soon as the test person has reached the calculated EHR, the test was finished.

The additional BFRE protocol was applied during the cycling exercise on both lower limbs periodically three times per leg for a duration of 1 min (first week) to 6 min (sixth week). While the AC group performed a sham-BFR exercise with a fixed value of 20 mmHg, the BFR-group was loaded with 40% of the individual limb occlusion pressure (LOP; right = 88.27 ± 8.46 mmHg, left = 87.32 ± 7.39 mmHg) (**Figure 1**).

To determine the LOP, the inflatable tourniquets of 11.5 cm width were placed proximal at the exercising legs before the training session (PBFR, Delfi medical Inc., Vancouver, Canada). After a 10-min rest period, LOP was determined sonographically in a lying position by displaying the femoral artery with an ultrasound device and using a Doppler to assess the blood flow within the vessel. Subsequently, the cuff was inflated until no further blood flow was detectable. This pressure was defined as the individual LOP.

Outcomes Measures

The examination battery consisted of general vital and anthropometric data, muscular function parameters, functional examinations, and questionnaire-based data collection.

Vital- and Anthropometric Data

At each time point, vital parameters like blood pressure (RR) and heart rate (HR) were recorded. Anthropometric data consist of recording body weight (BW), body height (BH) as well as the circumference of both thighs and calves for estimation of skeletal muscle mass of the lower extremities. To visualize the femoral circumference an anatomic reference line was drawn between the spina iliaca anterior superior and the margo superior patella. At 50% (FC-50) length of this reference line, the femoral circumference of both legs was determined. The calf circumference was determined after multiple measurements at the largest diameter. The measurement was performed three times at all points and the mean value was determined. Furthermore, the circumference of both knees was recorded to illustrate swelling pre- and postoperative. Measurement points were above the margo superior patellae, in the middle of the patella as well as above the apex patellae.

Muscular Strength

Muscular function in this study was analyzed by a unilateral six-repetition maximum test (6RM) of the leg-extension and leg-curl machine (Paoli et al., 2013). Following a warmup, a maximum of five trials separated by 5 min of recovery was allowed to obtain a true 6RM. With an accuracy of 1.00 kg, the highest load that the subject was able to lift six times to a knee extension of approximately zero degrees was accepted as 6RM.

Assessment of Function

The functionality of the participating patients was determined by active knee joint mobility (range of motion, ROM) as well as the chair-rising- (CRT) and 6-min walking test (6MWT). The ROM of the knee joint was determined in the supine position. A goniometer was used to measure the active extension and flexion of the knee joint (Bade et al., 2014). In CRT, the subject sits on an ordinary chair without armrests. With arms crossed on the chest, the test person performs as many stand-up and sit-down movements as he or she can manage within 30 s (Gill and McBurney, 2008). A complete repetition was then scored after the test person was in full extension while standing, as well as with a leaning back in a sitting position. The 6MWT is used to estimate and monitor cardiovascular and

TABLE 1 | Patient characteristics and surgical data for each group.

	CON (*N* = 10)	BFR (*N* = 10)	AC (*N* = 10)	One-way ANOVA (p/η_p^2)
Operated limb	Left: 4/Right: 6	Left: 9/Right: 1	Left: 4/Right: 6	-
Sex	Male: 6/Female: 4	Male: 7/Female: 3	Male: 7/Female: 3	-
Age (yr)	66.3 (7.1)	61.5 (8.8)	64.2 (7.7)	0.410/0.064
Height (cm)	175.4 (8.8)	178.4 (7.2)	175.3 (5.5)	0.565/0.041
Body weight (kg)	90.3 (17.5)	85.3 (15.3)	85.1 (16.5)	0.713/0.025
Blood pressure (mmHg)				
Systolic	129.9 (10.1)	127.5 (5.9)	124.7 (7.9)	0.629/0.034
Diastolic	81.7 (6.9)	81.5 (7.1)	80.8 (4.4)	0.448/0.058
Rest heart rate (bpm)	73.7 (7.2)	66.7 (6.9)	69.8 (7.6)	0.114/0.148
Duration of surgery (min)	111.7 (14.4)	112.3 (14.4)	109.6 (16.4)	0.916/0.006
Blood loss during surgery (mL)	174.0 (63.5)	185.0 (65.4)	168.0 (55.7)	0.824/0.014

Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group.

pulmonary performance below the anaerobic threshold. Participating patients walk for 6 minutes along a 20 m walkway. The goal for the patient is to complete as much distance as possible in the given time window. Individual pace changes and pauses are allowed. After 6 minutes, the time is stopped, and the walking distance is written down in meters.

Patient Self-Assessment Tools

To assess the subjectively experienced functional status, pain perception and quality of life of the patients, the Knee Injury and Osteoarthritis Outcome Score (KOOS) was used. KOOS contents of 42 questions in five different dimensions: Symptoms (seven questions), pain (nine questions), activities of daily living (17 questions), functionality in sports and recovery (five questions) and quality of life-related to the affected knee (four questions).

Statistics

Statistical analyses were performed using SPSS (SPSS, v.27, Chicago, IL, United States). Normal distribution and homogeneity of variance were verified using Shapiro-Wilk and Levene's Test, respectively. Potential group differences in baseline and surgical data (i.e., age, height, body weight, duration of surgery, etc.) were assessed using one-way ANOVAs. To compare the changes in measures over time among groups, two-way repeated-measures ANOVAs (rANOVAs; time x group) were performed. In case of significant time × group interactions, separate one-way repeated measures ANOVAs were used to analyze the simple main effects for time within each group. The mean differences between groups (i.e., simple main effects for group) within each time point were assessed using separate one-way ANOVAs. If the main effects for time or group were detectable, *post hoc*-tests with Bonferroni correction were performed to check which factor levels differ significantly from one another. For the interaction and main effects, the partial eta squared η_p^2 was calculated as effect strength measure and interpreted as follows (Cohen, 1988): a $\eta_p^2 \geq 0.01$: small effect, ≥ 0.06: medium effect, and ≥0.14: large effect. For all results, an alpha level of 0.05 was interpreted as statistically significant. To reduce investigator bias, data analysis was blinded to the evaluating researchers.

RESULTS

Table 1 presents the baseline and surgical data for each group. At baseline, there were no significant differences regarding their demographic data. In addition, the mean duration of surgery and blood loss during surgery did not differ among all groups.

Exercise Intensity and Physiological Responses During Prehabilitation

Table 2 summarizes the training data during phase 1 (session 1–6) and 2 (session 7–12) of the prehabilitation including exercise intensity, mean HR and RR during training and individual LOP measured before training. All patients in the training groups completed all planned training sessions during the 6-weeks prehabilitation period. The current study documented a dropout rate of 0% and no exercise or BFR-related adverse events. For exercise intensity, there were a significant time × group interaction ($p < 0.001$, $\eta_p^2 = 0.599$) and time effect (BFR-group: $p < 0.001$, $\eta_p^2 = 0.902$; AC-group: $p < 0.001$, $\eta_p^2 = 0.900$). *Post hoc*-tests revealed that the training intensity in both training groups significantly increased during the 2. phase of prehabilitation. No statistically noticeable changes in physiological measures during the training period were detected in any group (**Table 2**).

Estimation for Skeletal Muscle Mass of the Lower Extremities

Table 3 summarizes the femoral- and calf-circumference of both operated- (OP) and non-operated (NonOP) legs and their percent difference during the prehabilitation- and post-operative-period. Significant time × group interaction effects were indicated for all measured femoral circumference values ($p < 0.001$, $0.350 < \eta p2 < 0.494$). Further analyses revealed significant time effects in the BFR-group ($p < 0.001$, $0.674 < \eta_p^2 < 0.754$) and CON ($p \leq 0.001$, $0.627 < \eta_p^2 < 0.728$). The AC-group did not indicate any time effects ($p \geq 0.078$, $0.178 < \eta_p^2 < 0.262$). For the calf circumference, no changes were detected in any group despite of the significant interaction effect ($p = 0.018$, $\eta_p^2 = 0.205$) and main time effect in CON for the NonOP leg ($p = 0.013$, $\eta_p^2 = 0.426$). Post hoc-tests revealed

TABLE 2 | Measures related to training during the 6-weeks prehabilitation period of both training groups.

	BFR (*N* = 10)	AC (*N* = 10)	One-way ANOVA/rANOVA (p/η_p^2)				
			Time		Group		Time x group
			BFR	AC	Phase 1	Phase 2	
Exercise intensity (W)							
Phase 1 (session 1–6)	62.5 (17.5)	69.0 (17.5)	<0.001/0.902	<0.001/0.900	0.417/0.037	0.474/0.029	<0.001/0.599
Phase 2 (session 7–12)	81.8 (15.2)*	76.5 (15.2)*					
Mean heart rate during training (bpm)							
Phase 1 (session 1–6)	106 (10)	103 (10)	0.542/0.021		0.350/0.049		0.452/0.032
Phase 2 (session 7–12)	108 (11)	103 (11)					
Mean blood pressure during training (mmHg)							
Systolic							
Phase 1 (session 1–6)	143.0 (9.7)	135.9 (9.7)	0.015/0.288		0.053/0.192		0.209/0.086
Phase 2 (session 7–12)	147.2 (9.7)	137.4 (9.7)					
Diastolic							
Phase 1 (session 1–6)	82.5 (7.8)	81.4 (7.8)	0.040/0.214		0.723/0.007		0.890/0.001
Phase 2 (session 7–12)	84.3 (7.9)	83.1 (7.9)					
LOP-Left (mmHg)							
Phase 1 (session 1–6)	226 (14)	228 (14)	0.072/0.169		0.246/0.074		0.100/0.143
Phase 2 (session 7–12)	217 (11)	228 (11)					
LOP-Right (mmHg)							
Phase 1 (session 1–6)	228 (13)	229 (13)	0.024/0.254		0.389/0.042		0.075/0.166
Phase 2 (session 7–12)	220 (14)	228 (14)					

*Data are provided as mean (standard deviation). BFR, BFR-training group; AC, active control group; LOP, individual limb occlusion pressure; rANOVA, repeated-measures analysis of variance. *p < 0.05, significantly different to phase 1*

that the femoral circumference of both legs significantly increased in the BFR-group already at 3w-Prehab (p = 0.002). In addition, the BFR-group showed a further improvement in the femoral circumference of the OP leg after the prehabilitation period (p = 0.006). The CON did not indicate any changes in the femoral circumference during and after the prehabilitation period (p = 0.131). At 3m-Post-OP, both CON and BFR-group showed significantly decreased femoral circumference of both legs compared to the Pre-OP-level ($p \leq 0.017$), but the BFR-group still remained above the baseline level (p = 0.023). At 6m-Post-OP, all femoral circumference in the BFR-group increased again ($p \leq 0.030$) with significantly higher values compared to the baseline level ($p < 0.001$). In contrast, the CON demonstrated significantly reduced femoral circumference of both legs at 6m-Post-OP with significantly lower values compared to the pre-operative level ($p \leq 0.05$).

Regarding the percent difference between the OP and NonOP leg, significant time × group interaction effects were observed for the femoral circumference (p = 0.014, η_p^2 = 0.186), while for the calf circumference, there were no significant main or interaction effects (**Table 3**). Further analyses on percent difference in the femoral circumference revealed a significant time effect only for the CON (p = 0.002, η_p^2 = 0.469) and a significant group effect at the baseline (p = 0.037, η_p^2 = 0.217). Despite the absence of the significant time effects, both training groups indicated a decreased percent difference in the femoral circumference between both legs following the prehabilitation, which increased again during the post-operative period but not beyond the baseline level (**Table 3**). In contrast, the percent difference in the femoral circumference between both legs in the CON continually increased during the postoperative study period. It was higher at 6m-Post-OP than the baseline level (p = 0.013).

Knee Swelling Measurements

The knee circumference measured at three different places of both OP and NonOP legs during the prehabilitation- and postoperative-period are presented in **Table 4**. Regarding the knee circumference, we found no time × group interaction effects ($p > 0.059$, $0.060 < \eta_p^2 < 0.164$) except for the upper knee circumference of the Non-OP leg (p = 0.010, η_p^2 = 0.213), which indicated no further time or group effects (**Table 4**).

Further analyses revealed a significant time effect only for the lower knee circumference of the OP leg (p = 0.017, η_p^2 = 0.072), indicating that knee circumference increased at 3m-Post-OP and returned to baseline level at 6m-Post-OP.

Regarding the knee swelling accessed by the percent difference between OP and NonOP knee, a significant time × group interaction effect was found only for upper knee (p = 0.049, η_p^2 = 0.172). For the swelling measured at middle knee, we found a significant group effect (p = 0.046, η_p^2 = 0.211) indicating lower values in the BFR-group compared to other groups. For lower knee, found a significant time effect ($p < 0.001$, η_p^2 = 0.373) with a continually decreased swelling during the prehabilitation period, which increased at 3m-Post-OP and returned to baseline level at 6m-Post-OP.

Further analyses for the swelling measured at upper knee detected significant time effect only in the CON (p = 0.017, η_p^2 = 0.445). In addition, there were significant group effects at baseline ($p < 0.012$, η_p^2 = 0.280) and 3m-Post-OP ($p < 0.049$, η_p^2 = 0.200). At baseline, the upper knee swelling was significantly higher in the AC-group that the CON (p = 0.043), while the BFR-group did not differ to other groups ($p \geq 0.093$). The CON demonstrated a

TABLE 3 | Measures related to skeletal muscle mass of the lower extremities during the prehabilitation- and post-operative period.

	CON (*N* = 10)	BFR (*N* = 10)	AC (*N* = 10)	One-way ANOVA/rANOVA (p/η_p^2)								
				Time			Group					Time x group
				CON	BFR	AC	Baseline	3w-Prehab	Pre-OP	3m-Post-OP	6m-Post-OP	
Femoral circumference OP (cm)												
Baseline	58.2 (7.4)	53.2 (4.2)	52.0 (7.3)	<0.001/0.728	<0.001/0.754	0.078/0.266	0.092/0.162	0.224/0.105	0.331/0.079	0.524/0.047	0.592/0.038	<0.001/0.494
3w-Prehab	57.7 (7.5)	55.6 (4.6)[a]	52.5 (7.2)									
Pre-OP	57.6 (7.6)	57.0 (5.2) [ab]	53.4 (7.1)									
3m-Post-OP	55.9 (7.1) [abc]	55.0 (3.9) [ac]	52.8 (6.9)									
6m-Post-OP	55.5 (7.6) [abc]	56.6 (4.0) [ad]	53.7 (6.4)									
Femoral circumference NonOP (cm)												
Baseline	58.5 (7.2)	55.0 (4.0)	53.6 (7.3)	0.001/0.627	<0.001/0.674	0.192/0.178	0.229/0.103	0.311/0.083	0.365/0.072	0.502/0.050	0.510/0.049	<0.001/0.350
3w-Prehab	58.5 (7.2)	56.8 (4.4)[a]	54.0 (7.4)									
Pre-OP	58.5 (7.2)	57.6 (4.5)[a]	54.5 (7.3)									
3m-Post-OP	57.2 (7.2) [abc]	56.9 (4.3)[a]	54.2 (6.7)									
6m-Post-OP	57.4 (7.2) [abc]	58.0 (4.3) [ad]	55.0 (6.7)									
%Difference in femoral circumference NonOP - OP												
Baseline	-0.49 (3.24)	-3.44 (1.48)[e]	-3.09 (2.85)	0.002/0.469	0.059/0.254	0.271/0.135	0.037/0.217	0.523/0.047	0.802/0.016	0.748/0.021	0.654/0.031	0.014/0.186
3w-Prehab	-1.43 (3.54)	-2.29 (0.94)	-2.86 (3.16)									
Pre-OP	-1.64 (3.73)	-1.15 (2.74)	-2.11 (3.17)									
3m-Post-OP	-2.27 (4.18)	-3.44 (2.71)	-2.67 (3.44)									
6m-Post-OP	-3.44 (3.50)[a]	-2.54 (2.61)	-2.24 (2.80)									
Calf circumference OP (cm)												
Baseline	39.2 (3.5)	38.3 (3.9)	36.7 (2.7)		0.682/0.014				0.054/0.201			0.412/0.072
3w-Prehab	39.2 (3.5)	38.8 (3.6)	36.8 (2.7)									
Pre-OP	39.2 (3.5)	38.8 (3.7)	37.0 (2.7)									
3m-Post-OP	38.7 (3.8)	38.9 (3.8)	36.7 (2.7)									
6m-Post-OP	38.9 (4.0)	39.1 (3.4)	37.1 (2.7)									
Calf circumference NonOP (cm)												
Baseline	40.2 (3.5)	39.2 (3.4)	37.9 (3.4)	0.013/0.426	0.502/0.053	0.202/0.169	0.333/0.078	0.366/0.072	0.476/0.054	0.549/0.043	0.524/0.047	0.018/0.205
3w-Prehab	40.2 (3.5)	39.3 (3.4)	38.0 (3.4)									
Pre-OP	40.2 (3.5)	39.4 (3.5)	38.3 (3.4)									
3m-Post-OP	39.3 (3.9)	39.5 (3.5)	37.9 (3.3)									
6m-Post-OP	39.4 (3.8)	39.4 (3.6)	37.8 (3.3)									
%Difference in calf circumference NonOP - OP												
Baseline	-2.63 (3.34)	-2.53 (2.20)	-3.16 (4.46)		0.612/0.019				0.241/0.104			0.406/0.030
3w-Prehab	-2.63 (3.34)	-1.36 (1.42)	-3.20 (3.92)									
Pre-OP	-2.63 (3.34)	-1.54 (2.79)	-3.54 (4.04)									
3m-Post-OP	-1.63 (5.23)	-1.36 (2.84)	-3.02 (4.99)									
6m-Post-OP	-1.55 (2.93)	-0.67 (1.51)	-1.93 (4.22)									

Data are provided as mean (standard deviation). CON, control group; BFR = BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.

[a]$p < 0.05$, *significantly different to baseline within the respective group.*

[b]$p < 0.05$, *significantly different to 3w-Prehab within the respective group.*

[c]$p < 0.05$, *significantly different to Pre-OP within the respective group.*

[d]$p < 0.05$, *significantly different to 3m-Post-OP within the respective group.*

[e]$p < 0.05$, *significantly different to CON within the respective time point.*

greater increase in the upper knee swelling with higher level at 3m-Post-OP compared to the BFR-group ($p = 0.046$), which significantly decreased again at 6m-Post-OP ($p = 0.044$). Despite being statistically non-significant, both BFR- and AC-groups demonstrated decreased knee swelling values at 6m-Post-OP compared to the baseline level (**Table 4**).

Functionality Measurements

Table 5 summarizes the ROM assessed during active extension and flexion. For all ROM measurements, there were no significant time × group interaction effects ($p \geq 0.403$, $0.043 < \eta_p^2 < 0.073$). Further, significant time effects were detected only for OP leg (extension: $p = 0.012$, $\eta_p^2 = 0.138$; flexion: $p < 0.001$, $\eta_p^2 = 0.468$) indicating a continually improved ROM during overall study period. No main group effects were found for all ROM measures ($p \geq 0.169$, $0.048 < \eta_p^2 < 0.128$).

For 6-MWT (**Figure 2A**), we found a significant time × group interaction effect ($p = 0.012$, $\eta_p^2 = 0.209$). Further analyses revealed a significant time effect only in BFR-group ($p < 0.001$, $\eta_p^2 = 0.677$). *Post hoc*-tests for BFR-group indicated a significant improvement in 6-MWT already at 3w-Prehab compared to baseline (390 ± 82 m to 431 ± 69 m, $p = 0.034$), which increased further after the prehabilitation (to 456 ± 58 m) with a significantly higher level to the baseline- and 3w-Prehab-level ($p \leq 0.048$). At 3m-Post-OP, the BFR-group showed a significant deterioration in 6-MWT compared to Pre-OP (to 426 ± 73 m, $p = 0.05$), but it pronounced recuperated at 6m-Post-OP (to 464 ± 58 m, $p = 0.002$). Consequently, the BFR-group demonstrated a significantly higher ability in 6-MWT at 6m-Post-OP compared to baseline- ($p = 0.004$) and 3w-Prehab-level ($p = 0.007$).

Regarding the CRT (**Figure 2B**), there was a significant time x group effect ($p = 0.007$, $\eta_p^2 = 0.205$). In addition, we found significant time effects in BFR- ($p < 0.001$, $\eta_p^2 = 0.671$) and AC-group ($p < 0.001$, $\eta_p^2 = 0.596$), whereas no changes occurred in the CON. According to *Post hoc*-tests, the patients in the BFR-group significantly improved in the CRT already at 3w-Prehab compared to the baseline (8.90 ± 2.08 reps. to 11.20 ± 2.35 reps., $p = 0.012$). In comparison, the AC-group showed a significant improvement only after the prehabilitation period (9.90 ± 2.51 reps. to 12.00 ± 2.49 reps., $p = 0.006$). At 3m-Post-OP, the AC-group exhibited a significant deterioration in the CRT compared to Pre-OP (to 10.00 ± 2.98 reps., $p = 0.002$), which pronounced improved at 6m-Post-OP again (to 11.30 ± 2.50 reps., $p = 0.019$), and was significantly higher to baseline level ($p = 0.026$). In contrast, the BFR-group indicated no statistically significant change in the CRT at 3m-Post-OP (12.10 ± 2.73 reps. to 10.90 ± 2.77 reps., $p = 1.00$), which was still higher compared to the baseline level ($p = 0.038$). At 6m-Post-OP, the BFR-group improved again (to13.30 ± 2.31 reps., $p = 0.003$) remaining above the baseline- and 3w-Prehab level ($p \leq 0.004$).

Muscular Strength of the Lower Extremities

The results regarding the muscular strength of both OP and NonOP legs and their percent difference during the prehabilitation and post-operative period are presented in **Table 6**. Significant interaction effects were observed for all measured muscle strength indices ($p < 0.001$, $0.567 < \eta_p^2 < 0.625$). Further analyses revealed a significant main time effect for all muscle strength measures in all groups ($p < 0.05$, $0.298 < \eta_p^2 < 0.916$). In addition, there were significant group effects for all measured leg strength indices ($p \leq 0.046$, $0.204 < \eta_p^2 < 0.676$) excepting for leg extension of OP leg at baseline ($p = 0.077$, $\eta_p^2 = 0.173$) and at 3w-Prehab ($p = 0.230$, $\eta_p^2 = 0.103$). *Post hoc*-tests revealed that both training groups significantly improved in all measured leg strength indices already at 3w-Prehab (BFR-group: $p \leq 0.01$; AC-group: $p \leq 0.026$). At Pre-OP, the BFR-group indicated more pronounced improvements in all leg strength measures (i.e., 3w-Prehab to Pre-OP: $p < 0.001$) with significantly higher values compared to other groups ($p < 0.05$). No changes occurred in the CON during the prehabilitation period ($p = 0.100$). At 3m-Post-OP, significant reductions in leg strength measures were observed in BFR-group ($p \leq 0.01$) except for the leg extension of the NonOP leg ($p = 0.308$), which were still above the baseline level ($p \leq 0.01$). The AC-group indicated significantly decreased muscular strength in both leg-extension (only in NonOP leg) and -curl (in both legs) at 3m-Post-OP even to the baseline level ($p \leq 0.05$). Similarly, the patients in the CON showed a significant decrement in leg extension of both OP and NonOP legs at 3m-Post-OP with a lower value compared to the pre-operative level ($p \leq 0.031$). At the same time, no changes occurred in leg curl ($p \geq 0.187$). At 6m-Post-OP, both training groups significantly improved again in all leg strength measures (BFR-group: $p \leq 0.029$; AC-group: $p \leq 0.031$) with a significant difference to baseline- (BFR-group: $p < 0.001$ for all measures; AC-group: $p \leq 0.029$ only for leg curl of both legs) and to 3w-Prehab-level (only in BFR-group: $p \leq 0.038$ for all measures). The CON also indicated significant improvements but only in muscular strength of OP leg (leg extension: $p = 0.005$; leg curl: $p = 0.007$). Consequently, there were significant differences in leg strength between BFR-group and other groups during the overall post-operative period (AC-group: $p \leq 0.032$; CON: $p \leq 0.020$) excepting for the leg extension of OP leg at 3m-post-OP between BFR-group and CON ($p = 0.265$).

Regarding the strength deficit of the OP leg accessed by the percent difference between OP and Non-OP leg during leg-extension and -curl, we found no significant interaction ($p \geq 0.063$, $0.134 < \eta_p^2 < 0.150$) and time effects ($p \geq 0.105$, $0.038 < \eta_p^2 < 0.081$). There were significant main group effects ($p \leq 0.003$, $0.366 < \eta_p^2 < 0.481$) with lower values in BFR-group compared to other groups.

Subjective Surveys and Questionnaires

The analysis on the KOOS (**Figure 3**) demonstrated significant time × group interaction effects for all evaluated dimensions ($p \leq 0.004$, $0.268 < \eta_p^2 < 0.416$). Further analyses revealed a significant main time effect for all measures of KOOS in all groups (CON: $p \leq 0.004$, $0.475 < \eta_p^2 < 0.907$; BFR-group: $p < 0.001$, $0.869 < \eta_p^2 < 0.978$; AC-group: $p \leq 0.001$, $0.571 < \eta_p^2 < 0.951$). In addition, there were significant group effects for all measures of KOOS ($p \leq 0.049$, $0.200 < \eta_p^2 < 0.581$) excepting for the dimension *symptoms* at baseline, 3w-Prehab, 3m-Post-OP, and 6m-Post-OP ($p \geq 0.207$, $0.029 < \eta_p^2 < 0.110$) and *quality of life-related to the affected knee* at baseline ($p = 0.398$, $\eta_p^2 = 0.066$).

TABLE 4 | Measures related to knee swelling during the prehabilitation- and post-operative period.

	CON (*N* = 10)	BFR (*N* = 10)	AC (*N* = 10)	One-way ANOVA/rANOVA (p/η_p^2)							
				Time			Group					Time x group
				CON	BFR	AC	Baseline	3w-Prehab	Pre-OP	3m-Post-OP	6m-Post-OP	
Upper knee circumference OP (cm)												
Baseline	45.0 (4.5)	44.0 (3.1)	43.9 (4.1)		0.686/0.014				0.323/0.083			0.505/0.060
3w-Prehab	45.0 (4.5)	43.7 (3.4)	43.4 (4.0)									
Pre-OP	45.0 (4.5)	43.7 (3.8)	43.3 (4.2)									
3m-Post-OP	46.0 (5.0)	44.3 (3.3)	43.8 (4.2)									
6m-Post-OP	44.8 (5.1)	43.9 (3.4)	43.6 (4.2)									
Upper knee circumference NonOP (cm)												
Baseline	44.5 (3.8)	43.3 (3.0)	42.2 (3.1)	0.057/0.287	0.069/0.209	0.278/0.129	0.485/0.052	0.509/0.049	0.600/0.037	0.793/0.017	0.805/0.016	0.010/0.213
3w-Prehab	44.5 (3.8)	43.2 (3.3)	42.4 (4.0)									
Pre-OP	44.5 (3.8)	43.8 (3.8)	42.6 (4.2)									
3m-Post-OP	44.0 (5.5)	43.6 (3.1)	42.7 (4.1)									
6m-Post-OP	43.7 (5.3)	43.7 (3.3)	42.6 (4.1)									
%Difference upper knee NonOP - OP												
Baseline	1.22 (2.04)	1.78 (1.81)	3.90 (2.01)[e]	0.017/0.445	0.073/0.239	0.093/0.250	0.012/0.280	0.181/0.119	0.076/0.174	0.049/0.200	0.097/0.159	0.049/0.172
3w-Prehab	1.22 (2.04)	1.62 (1.48)	2.65 (1.63)									
Pre-OP	1.22 (2.04)	0.31 (1.04)	1.96 (1.40)									
3m-Post-OP	4.39 (2.31)*	1.77 (1.51)	2.84 (2.79)									
6m-Post-OP	2.64 (1.78)[d]	1.09 (0.74)	2.79 (2.59)									
Middle knee circumference OP (cm)												
Baseline	43.8 (4.5)	42.7 (3.2)	42.7 (3.2)		0.172/0.065				0.096/0.165			0.134/0.123
3w-Prehab	43.8 (4.5)	42.4 (2.5)	42.2 (3.2)									
Pre-OP	43.8 (4.5)	42.4 (2.9)	42.1 (3.3)									
3m-Post-OP	44.8 (4.1)	42.7 (2.7)	42.6 (3.0)									
6m-Post-OP	43.6 (4.0)	41.8 (2.9)	42.4 (2.9)									
Middle knee circumference NonOP (cm)												
Baseline	42.9 (4.5)	41.5 (3.4)	41.0 (3.9)		0.563/0.024				0.264/0.097			0.555/0.058
3w-Prehab	42.9 (4.5)	41.8 (3.6)	41.2 (3.9)									
Pre-OP	42.9 (4.5)	41.7 (3.7)	41.2 (4.1)									
3m-Post-OP	42.7 (5.4)	41.8 (3.2)	41.2 (4.0)									
6m-Post-OP	42.3 (5.2)	41.6 (3.3)	41.1 (4.1)									
%Difference middle knee NonOP - OP												
Baseline	1.87 (1.74)	2.85 (2.24)	4.20 (1.41)		0.140/0.072				0.046/0.211			0.107/0.133
3w-Prehab	1.87 (1.74)	1.54 (2.24)	2.58 (1.78)									
Pre-OP	1.87 (1.74)	1.82 (2.67)	2.05 (1.75)									
3m-Post-OP	4.86 (2.94)	2.27 (1.75)	3.25 (4.00)									
6m-Post-OP	3.14 (2.18)	0.75 (2.65)	3.19 (2.96)									
Lower knee circumference OP (cm)												
Baseline	39.4 (3.5)	38.5 (3.4)	39.0 (3.2)		0.017/0.149				0.067/0.188			0.059/0.164
3w-Prehab	39.4 (3.5)	37.8 (3.1)	38.7 (3.3)									
Pre-OP	39.4 (3.5)	37.7 (3.8)	38.6 (3.3)									
3m-Post-OP	40.3 (4.1)	38.6 (3.4)	38.6 (3.3)									
6m-Post-OP	39.4 (4.0)	38.3 (3.7)	38.8 (3.2)									
Lower knee circumference NonOP (cm)												
Baseline	39.0 (3.6)	37.5 (3.1)	37.5 (3.3)		0.335/0.008				0.335/0.081			0.384/0.076
3w-Prehab	39.0 (3.6)	37.3 (2.8)	37.4 (3.3)									
Pre-OP	39.0 (3.6)	37.3 (3.0)	37.7 (3.3)									
3m-Post-OP	38.8 (4.1)	37.3 (2.7)	37.7 (3.3)									
6m-Post-OP	38.7 (3.9)	37.4 (2.8)	37.7 (3.1)									
%Difference lower knee NonOP - OP												
Baseline	0.76 (3.51)	2.60 (1.89)	3.83 (2.16)		<0.001/0.373				0.573/0.042			0.282/0.091
3w-Prehab	0.76 (3.51)	1.39 (2.00)	3.49 (2.58)									
Pre-OP	0.76 (3.51)	1.04 (1.89)	2.54 (1.78)									
3m-Post-OP	4.06 (2.42)	3.51 (2.65)	2.32 (3.30)									
6m-Post-OP	1.90 (1.55)	2.30 (2.25)	2.94 (2.21)									

Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.

[a] $p < 0.05$, *significantly different to baseline within the respective group.*

[b] $p < 0.05$, *significantly different to 3w-Prehab within the respective group.*

[c] $p < 0.05$, *significantly different to Pre-OP within the respective group.*

[d] $p < 0.05$, *significantly different to 3m-Post-OP within the respective group.*

[e] $p < 0.05$, *significantly different to CON within the respective time point.*

Post hoc-tests for the KOOS related to *symptoms* (**Figure 3A**) revealed a significant improvement only in the BFR-group during (45.0 ± 5.4 to 54.2 ± 3.9, $p < 0.001$) and after the prehabilitation period (to 60.8 ± 3.7, $p < 0.001$) with a significant higher value compared to other groups at Pre-OP (CON: 51.7 ± 4.7; AC-group: 48.6 ± 9.5, $p \leq 0.01$). No difference was observed between CON and AC-group ($p = 0.893$). At 3m-Post-OP, the BFR-group indicated a significant lower KOOS related to *symptoms* (47.2 ± 3.0) compared to 3w-Prehab- ($p = 0.021$) and Pre-OP-level ($p < 0.001$), but still similar level to other groups (CON: 45.0 ± 4.5; AC-group: 46.1 ± 7.7). At 6m-Post-OP, the KOOS related to *symptoms* increased in all groups (CON: 63.4 ± 5.1; BFR-group: 67.1 ± 3.6; AC-group: 65.2 ± 9.0) with a significantly higher value compared to previous level ($p \leq 0.05$).

The KOOS related to *pain* (**Figure 3B**) in the CON was significantly higher at baseline compared to other groups (CON: 48.7 ± 3.9; BFR-group: 41.1 ± 4.3; AC-group: 44.2 ± 3.8, $p \leq 0.048$), but there was no difference between both training groups ($p = 0.299$). The BFR-group significantly improved the KOOS related to *pain* during (to 52.8 ± 4.1, $p < 0.001$) and after the prehabilitation period (to 57.6 ± 3.4, $p < 0.001$), while no changes occurred in the CON (at 3w-Prehab: 48.0 ± 4.1; at Pre-OP: 47.6 ± 5.4, $p = 1.00$). The AC-group showed an improvement in the KOOS related to *pain* only after the prehabilitation (i.e., at Pre-OP to 49.8 ± 5.2) with a significant difference to baseline ($p = 0.033$). Consequently, the BFR-group exhibited significant higher KOOS related to *pain* compared to other groups both at 3w-Prehab ($p \leq 0.048$) and at Pre-OP ($p \leq 0.003$). During the post-operative period, all groups indicated further improvements in the KOOS related to *pain* with a significant higher value to all pre-operative time points (at 3m-Post-OP: 60.8 ± 6.9 vs. 67.8 ± 3.5 vs. 61.7 ± 6.8; at 6m-Post-OP: 70.0 ± 4.7 vs. 76.2 ± 3.6 vs. 71.1 ± 7.9 in CON, BFR-, AC-group, respectively). In addition, the BFR-group indicated a significant higher KOOS related to *pain* during the post-operative period compared to the CON ($p \leq 0.050$ at both 3m- and 6m-Post-OP), whereas the AC-group did not differ to any other groups ($p \geq 0.10$).

The analysis on the KOOS related to the *activities of daily living* (**Figure 3C**) revealed a continuous improvement in both training groups during the overall study period (BFR-group: 45.5 ± 4.2 to 53.5 ± 6.1 to 57.9 ± 3.7 to 63.7 ± 5.1 to 71.9 ± 3.1; AC-group: 46.7 ± 3.5 to 50.5 ± 3.8 to 52.8 ± 3.4 to 59.0 ± 3.5 to 67.8 ± 3.1; $p \leq 0.047$), while the CON showed a significant improvement only during the post-operative period (49.2 ± 4.2 to 49.0 ± 4.4 to 49.4 ± 6.0 to 58.7 ± 4.5 to 65.6 ± 4.6; $p < 0.001$). Moreover, the BFR-group indicated significant higher KOOS related to activities of daily living compared to other groups at Pre-OP ($p \leq 0.05$), 3m- ($p \leq 0.05$), and 6m-Post-OP ($p \leq 0.05$), whereas no differences were observed between CON and AC-group ($p \geq 0.325$).

Regarding the functionality in sports and recovery (**Figure 3D**), the CON showed a higher KOOS compared to BFR-group at the baseline (24.0 ± 3.2 vs. 19.5 ± 3.7; $p = 0.024$), but the AC-group indicated no difference to any other groups (20.5 ± 3.7; $p \geq 0.105$). Only in the BFR-group, the functionality in sports and recovery already improved at 3w- Prehab (to 27.5 ± 3.5; $p = 0.001$) with a significant higher value compared to AC-group (22.5 ± 3.5; $p = 0.024$). At the Pre-OP, both training groups demonstrated higher sports and recovery functionality than the baseline level (BFR-group: to 29.5 ± 3.7; AC-group: to 24.0 ± 3.9; $p \leq 0.013$). No changes occurred in the CON during (to 25.0 ± 4.1) and after (to 25.0 ± 4.1) the prehabilitation period. At the 3m-Post-OP, only in the BFR-group, the functionality in sports and recovery was higher compared to the baseline level (to 31.0 ± 5.7; $p < 0.001$). At the 6m-Post-OP, the functionality in sports and recovery in the BFR-group was significant higher compared to each of all other time points (38.5 ± 3.4; $p \leq 0.003$), whereas the CON (32.0 ± 6.7) and AC-group (29.5 ± 6.0) demonstrated a significant higher value only compared to the baseline- ($p \leq 0.031$) and 3m-Post-OP-level ($p \leq 0.037$). After the Pre-OP until 6m-Post-OP, the functionality in sports and recovery was higher in the BFR-group compared to other group ($p \leq 0.05$).

The KOOS related to the quality of life-related to the affected knee (**Figure 3E**) increased in both training groups already at 3w-Prehab (BFR-group: 21.9 ± 3.3 to 33.8 ± 4.4; AC-group: 24.5 ± 5.3 to 28.5 ± 5.5; $p \leq 0.017$), and thus the BFR-group indicated higher value compared to the CON (25.5 ± 8.6; $p = 0.024$). At Pre-OP, the BFR-group demonstrated a more pronounced improvement in the quality of life-related to the affected knee (to 40.0 ± 3.2; $p = 0.011$) with a higher value compared to other groups (CON: to 25.6 ± 10.0; AC-group: 30.9 ± 5.2; $p \leq 0.017$). During the post-operative period, all groups demonstrated an increased quality of life-related to the affected knee compared to each of other previous time points (CON: to 45.6 ± 9.2 to 54.4 ± 8.99; BFR-group: to 52.5 ± 6.8 to 69.4 ± 4.6; AC-group: to 44.4 ± 4.6 to 55.0 ± 4.0; $p \leq 0.032$), whereas the BFR-group still exhibited higher values compared to other groups ($p \leq 0.05$) except for 3m-Post-OP in the CON ($p = 0.119$).

DISCUSSION

The present study aimed to investigate the impact of a 6-week prehabilitation with BFRE on skeletal muscle mass and strength before and after elective primary TKA. The main findings were, that BFR prehabilitation can reduce perceived pain and increase muscle mass and strength significantly more than prehabilitation without BFR before elective TKA surgery. Furthermore, BFR prehabilitation shows a positive influence on postoperative regeneration of skeletal muscle mass, strength and functionality compared to AC and CON, with supportive effects on subjective pain perception and QoL as well.

The present findings at baseline show that muscle mass and strength of patients receiving primary TKA is highly affected by OA. In addition to the subjectively perceived and objectively measurable decrease in functionality, the difference between the patients' extremities is particularly remarkable. Our data show significant differences between the muscle mass as well as muscle strength between the OP and NonOP leg at baseline (**Table 3**, **6**). These results are of particular significance, since it is known that the most important predictive parameters concerning a successful rehabilitation after surgery are preoperative strength, ROM, perceived pain and the ability to complete functional tasks (Topp et al., 2009). This condition is expected to be caused by

preoperative immobility and OA-induced arthrogenic muscle inhibition (Mayer et al., 2017). Since comparative literature show similar preoperative deficits (Ikeda et al., 2005; Dreyer et al., 2013), this circumstance could contribute to the dissatisfaction rate of approximately 20% after primary TKA (Bourne et al., 2010; Canovas and Dagneaux, 2018). Therefore, preoperative modification of physical capacities could be a tool to increase rehabilitation success and satisfaction after TKA.

Several studies supported preoperative well-being and postoperative rehabilitation through prehabilitation (Walls et al., 2010; Shaarani et al., 2013; Calatayud et al., 2017). However, current meta-analyses show only a slight to moderate influence of previous prehabilitation concepts on pre- and postoperative clinical outcomes (Wang et al., 2016; Moyer et al., 2017). These results are essentially influenced by the fact that existing methods of exercise led to increased pain, have been simplified and thus do no longer provide the necessary stimulus for muscle development. BFR training avoids this problem by using metabolic rather than mechanical stimuli to increase muscle mass and strength.

The present study suggests that prehabilitation with a 6-week cycling ergometer protocol is sufficient to enhance muscle mass, strength and subjective pain significantly before surgery. In comparison, BFRE was able to increase muscle mass already after 3 weeks of prehabilitation (**Table 3**), enhance muscle strength (**Table 6**) and functional performance (**Figure 1**) superior to AC. These findings are well in line with the literature, illustrating that a 6-week knee extensor-based prehabilitation protocol with BFR induce significant improvements in muscle mass and strength in patients receiving ACL-reconstruction (Kacin et al., 2021). Even though only an indirect measurement tool was chosen to represent muscle mass in the present study, these results allow the interpretation that changes in leg circumference are primarily explained by muscular gains. Furthermore, comparison between the OP and NonOP legs revealed, that BFR-prehabilitation can address successfully preoperative muscular disbalances (**Table 3**, **6**). In addition to the choice of exercise technique, the duration of the prehabilitation is also very important. In a study by Grapar Zargi and colleagues (Grapar Zargi et al., 2016), five times of BFRE within 10 days before an elective ACL reconstruction could not show any influence on the muscle mass and muscle strength. Considering the present results, a prehabilitation duration between three and 6 weeks with strength or endurance BFRE seems to be able to induce significant muscular effects before an elective joint surgery.

The improvements in muscle mass and strength of the BFR-group during and after the prehabilitation phase were associated with an equal enhancement in all five different subparameters of the KOOS score (**Figure 3**). These findings are well in line with previous literature reporting the positive influence of increased muscle mass and strength on subjective pain perception and QoL in OA-affected patients (Davison et al., 2017; Kemnitz et al., 2017). A meta-analysis by Ferlito et al. (2020)) was able to show that BFRE leads to similar gains in muscle mass and strength with concurrent reductions in perceived pain like high-intensity training. Although there is no high-intensity comparison group in the current study, our data are well in line with previous reports showing that low-intensity exercise with BFR is superior to low-intensity exercise alone (Segal et al., 2015). Especially the effects on pain perception during and after the prehabilitation protocol makes BFR training particularly interesting for patients with degenerative joint diseases. Our results show a significant reduction in pain during the 6-week prehabilitation period in patients with terminal gonarthrosis. These findings are well in line with the literature, showing significant reductions in pain in traumatic and degenerative triggered joint diseases by BFR (van Cant et al., 2020; Pitsillides et al., 2021). Since pain is one of the main symptoms in gonarthrosis (Jones et al., 2000) and can serve as a predictor of mortality during a 10-years post-surgery period (Dennis et al., 2016), the present results of pre- and postoperative pain reduction through BFR-prehabilitation are of particular importance.

Although, scientific knowledge about the underlying mechanisms and safety of BFRE is rising in the last years, a regular implementation of BFRE in clinical settings is not given at present. Therefore, it is important to note that the BFR application in this study was done without evoking adverse effects or leading to a drop out by concurrent rising patient compliance to this training method. The study protocol consists of an individual approach in BFR application (Patterson et al., 2019) by measuring the LOP before prehabilitation and applying a pneumatic-controlled pressure individualized to the LOP of the patient with a tourniquet of 11.5 cm wide. Regarding the necessary BFR pressure to induce muscular effects, there is an ongoing debate. While results from Ilett and colleagues (Ilett et al., 2019) show that most beneficial acute effects are induced by a pressure application of ≥60% of LOP, Counts et al. (2016) reported by regular application, that pressures of 40% LOP are also sufficient for hypertrophy effects. In our study, a BFR pressure of 40% LOP was applied to ensure high patient compliance to the exercise. Based on the positive results of this study, it can be concluded that in case of a reduced training status of the muscles of a subject, low BFR pressures such as 40% LOP are sufficient enough to induce significant effects on muscle mass and strength. Based on this individualized approach of BFRE, it is possible to provide a safe, patient compliant and efficient training for patients with end-stage gonarthrosis.

Although BFRE has demonstrated positive results in postoperative rehabilitation after anterior cruciate ligament reconstruction or conservative therapy of degenerative diseases of the knee joint (Charles et al., 2020), its use as a prehabilitation strategy in degenerative joint diseases has not been previously investigated. As the participating patients of the prehabilitation groups underwent surgery with enhanced muscle mass and strength, we could thereby also address the issue of the "better in, better out" principle.

First of all, the present study reported the classical course of regeneration of skeletal muscle mass and strength after primary TKA in all groups with an initial decrease after surgery (**Table 3**, **6**), and inverse improvement in perceived pain (**Figure 3**) (Mizner R. L. et al., 2005). However, even if the BFR-group follows this trend as well, our results show that the drop in muscle mass and strength 3 months after surgery does not fall below the baseline values. In comparison to the AC-group,

TABLE 5 | Active range of motion of knee joint during the prehabilitation- and post-operative period.

	CON (*N* = 10)	BFR (*N* = 10)	AC (*N* = 10)	One-way ANOVA/rANOVA (p/η_p^2)							
				Time			Group					Time x group
				CON	BFR	AC	Baseline	3w-Prehab	Pre-OP	3m-Post-OP	6m-Post-OP	
ROM extension OP (°)												
Baseline	2.60 (1.90)	3.40 (3.20)	2.40 (2.76)	0.012/0.138					0.169/0.128			0.723/0.043
3w-Prehab	2.60 (1.90)	2.70 (2.83)	2.30 (2.83)									
Pre-OP	2.60 (1.90)	2.70 (2.41)	2.30 (2.83)									
3m-Post-OP	3.30 (2.98)	1.50 (3.24)	2.00 (1.63)									
6m-Post-OP	2.00 (2.58)	0.70 (1.57)	1.20 (1.14)									
ROM extension NonOP (°)												
Baseline	3.90 (4.23)	0.30 (0.95)	1.20 (1.75)	0.607/0.022					0.699/0.027			0.580/0.056
3w-Prehab	3.90 (4.23)	0.70 (1.49)	0.90 (1.52)									
Pre-OP	3.90 (4.23)	0.50 (1.08)	1.70 (2.67)									
3m-Post-OP	2.60 (3.57)	1.20 (2.10)	1.30 (1.49)									
6m-Post-OP	1.10 (1.45)	0.20 (0.63)	0.60 (1.07)									
ROM flexion OP (°)												
Baseline	116.5 (14.8)	113.7 (11.5)	113.1 (4.2)	<0.001/0.468					0.513/0.048			0.403/0.073
3w-Prehab	116.4 (14.3)	116.2 (10.8)	112.7 (3.5)									
Pre-OP	117.0 (14.4)	116.0 (10.7)	112.4 (3.1)									
3m-Post-OP	114.7 (7.1)	117.9 (6.0)	113.3 (10.1)									
6m-Post-OP	122.0 (8.5)	119.5 (6.6)	115.3 (7.9)									
ROM flexion NonOP (°)												
Baseline	127.3 (9.8)	128.1 (9.1)	126.4 (7.7)	0.337/0.043					0.342/0.082			0.820/0.033
3w-Prehab	127.3 (9.8)	130.3 (8.5)	127.7 (6.9)									
Pre-OP	127.3 (9.8)	128.5 (8.6)	126.4 (8.0)									
3m-Post-OP	126.8 (9.5)	130.5 (10.5)	126.6 (9.2)									
6m-Post-OP	127.3 (10.1)	128.5 (8.6)	126.6 (9.2)									

Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.

[a]p < *0.05, significantly different to baseline within the respective group.*

[b]p < *0.05, significantly different to 3w-Prehab within the respective group.*

[c]p < *0.05, significantly different to CON within respective the time point.*

which showed a reduction in muscle mass and strength to baseline, or CON, which partly dropped below the baseline levels, patients of the BFR-group remain consistently better 3 months after TKA than before the start of the prehabilitation-phase (**Table 3**, **6**). Since these results are associated with an improved CRT 3 months post-surgery of the BFR-group in comparison to the other groups, it can be concluded that prehabilitation with BFRE shows a supportive impact on muscle and functional maintenance after TKA surgery. These changes lead to improved outcomes in the early rehabilitation

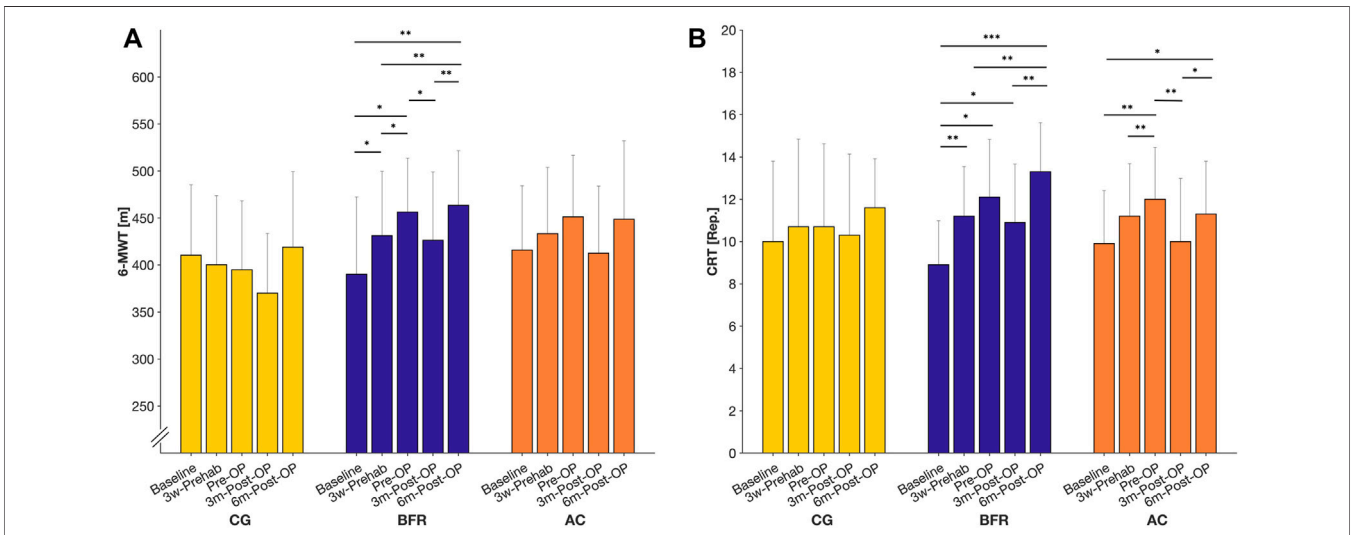

FIGURE 2 | Measures related to the 6-min walking test (6-MWT; **(A)** and chair-rising test (CRT; **(B)** during prehabilitation- and post-operative period. Data are provided as mean (standard deviation). CON = control group; BFR = BFR-training group; AC = active control group. ***p < 0.001, **p < 0.01, *p < 0.05, significant difference within the respective group.

TABLE 6 | Measures related to muscular strength of lower extremities during the prehabilitation- and post-operative period.

				One-way ANOVA/rANOVA (p/η_p^2)								
				Time					Group			Time x group
	CON (*N* = 10)	BFR (*N* = 10)	AC (*N* = 10)	CON	BFR	AC	Baseline	3w-Prehab	Pre-OP	3m-Post-OP	6m-Post-OP	
Leg extension OP (kg)												
Baseline	20.3 (8.1)	13.8 (9.1)	11.8 (7.8)	0.001/0.591	<0.001/0.863	0.014/0.392	0.077/0.173	0.230/0.103	0.003/0.351	0.033/0.223	0.002/0.364	<0.001/0.614
3w-Prehab	20.3 (7.1)	21.9 (9.1)a	15.3 (9.8)a									
Pre-OP	20.3 (7.1)[f]	31.5 (10.4) [ab]	16.0 (10.2)[a]f									
3m-Post-OP	15.0 (6.3) [abc]	22.1 (10.4) [ac]	11.1 (9.5)f									
6m-Post-OP	18.5 (7.0)[d]f	30.8 (11.1) [abd]	15.3 (9.4)[d]f									
Leg extension NonOP (kg)												
Leg extension NonOP (kg)				0.018/0.404	<0.001/0.851	0.003/0.503	0.026/0.237	0.021/0.250	0.003/0.348	0.002/0.379	0.000/0.445	<0.001/0.587
Baseline	28.3 (10.4)	24.3 (7.3)	17.5 (7.1)e									
3w-Prehab	28.5 (10.5)	31.8 (7.6)a	20.3 (8.1)[a]f									
Pre-OP	28.3 (10.7)f	38.4 (9.7) [ab]	22.0 (8.7)[a]f									
3m-Post-OP	22.5 (8.6) [abc]f	34.1 (8.5)a	18.8 (9.2)[c]f									
6m-Post-OP	27.0 (9.5)f	39.6 (9.7) [abd]	20.8 (8.3)[d]f									
%Difference leg extension NonOP - OP												
Baseline	-34.4 (36.0)	-64.6 (31.9)	-51.0 (31.3)	0.367/0.038						0.003/0.366		0.063/0.150
3w-Prehab	-33.1 (26.2)	-40.3 (23.2)a	-39.6 (35.9)									
Pre-OP	-31.9 (28.5)	-21.0 (16.2) [ab]	-44.1 (42.5)									
3m-Post-OP	-39.5 (34.0)	-46.7 (29.2)c	-69.1 (40.7)									
6m-Post-OP	-37.0 (28.4)	-27.3 (23.9) [abd]	-38.1 (26.8)									
Leg curl OP (kg)												
Baseline	10.8 (3.1)	9.0 (4.6)	6.4 (3.4)e	0.038/0.334	<0.001/0.916	0.003/0.502	0.046/0.204	0.017/0.260	<0.001/0.557	0.001/0.416	<0.001/0.645	<0.001/0.625
3w-Prehab	10.8 (3.1)	14.2 (4.6)a	9.0 (3.6)[a]f									
Pre-OP	11.0 (2.9)f	19.1 (4.8) [ab]	9.8 (3.6)[a]f									
3m-Post-OP	8.8 (2.7)f	14.6 (5.3) [ac]	6.4 (4.6)[c]f									
6m-Post-OP	11.0 (1.7)[d]f	19.6 (4.1) [abd]	9.0 (4.3) [ad]f									
Leg curl NonOP (kg)												
Baseline	13.3 (4.6)	14.6 (3.9)	10.0 (3.1)f	0.049/0.298	<0.001/0.815	<0.001/0.617	0.039/0.213	0.011/0.286	<0.001/0.550	<0.001/0.597	<0.001/0.676	<0.001/0.567
3w-Prehab	13.8 (4.3)f	19.0 (4.3)a	13.3 (4.4)[a]f									
Pre-OP	13.5 (4.3)f	23.1 (3.7) [ab]	14.5 (4.2)[a]f									
3m-Post-OP	11.3 (2.7)f	19.5 (3.1) [ac]	10.8 (4.4) [bc]f									
6m-Post-OP	12.8 (4.0)f	22.6 (2.6) [abd]	12.5 (3.5) [ad]f									
%Difference leg curl NonOP - OP												
Baseline	-19.8 (25.97)	-54.5 (35.5)	-54.4 (40.3)	0.105/0.081						<0.001/0.481		0.100/0.134
3w-Prehab	-24.5 (18.5)	-30.8 (27.5)	-39.9 (27.0)									
Pre-OP	-19.8 (18.9)	-20.4 (17.3)	-40.9 (23.0)									
3m-Post-OP	-26.5 (19.3)	-33.0 (29.5)	-67.5 (38.4)									
6m-Post-OP	-12.0 (19.9)	-15.8 (18.7)	-40.2 (28.5)									

Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group; rANOVA, repeated-measures analysis of variance; OP, operated leg; NonOP, non-operated leg.

[a]p < *0.05, significantly different to baseline within the respective group.*

[b]p < *0.05, significantly different to 3w-Prehab within the respective group.*

[c]p < *0.05, significantly different to Pre-OP within the respective group.*

[d]p < *0.05, significantly different to 3m-Post-OP within the respective group.*

[e]p < *0.05, significantly different to CON within the respective time point.*

[f]p < *0.05, significantly different to BFR-group within the respective time point.*

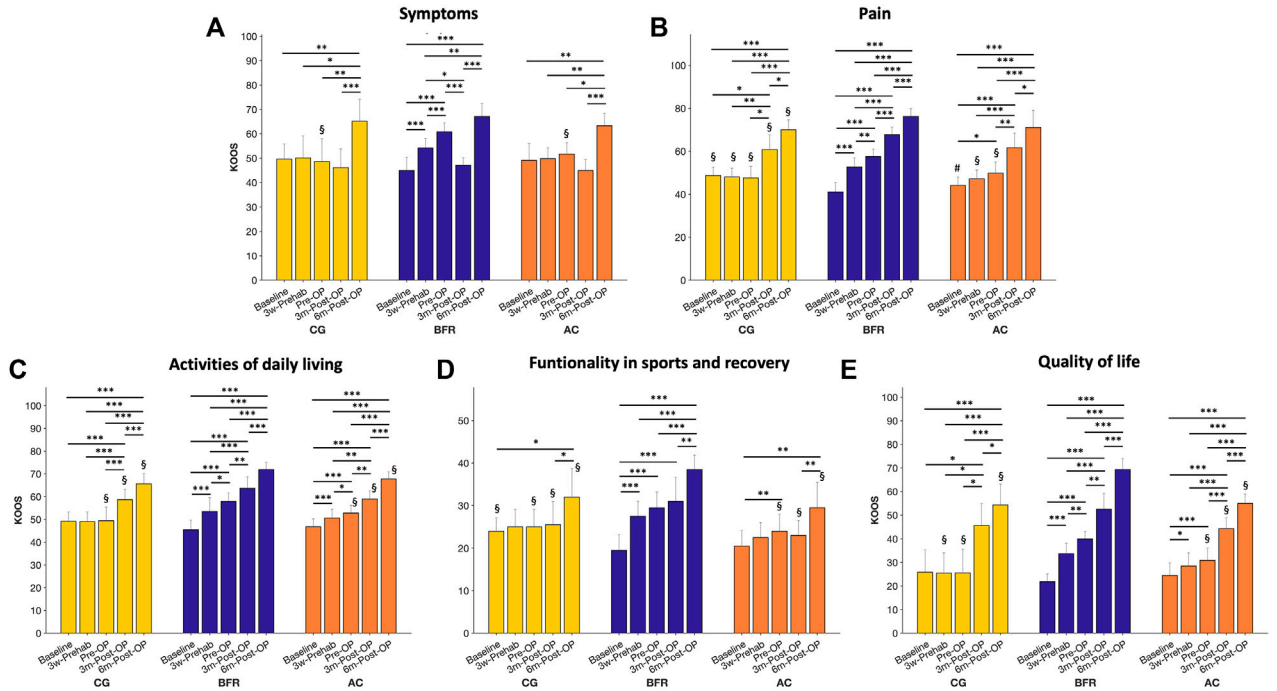

FIGURE 3 | Presentation of the five subparameters (Symptoms, Pain, Activities of daily living, Functionality in sports and recovery, Quality of life) of the Knee Injury and Osteoarthritis Outcome Score (KOOS) during prehabilitation- and post-operative period. Data are provided as mean (standard deviation). CON, control group; BFR, BFR-training group; AC, active control group. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$, significant difference within the respective group. $^{§}p < 0.05$, significantly different to BFR-group within the respective timepoint. $^{\#}p < 0.05$, significantly different to CON within the respective timepoint.

phase which is also illustrated by higher scores in the KOOS (**Figure 3**).

After 6 months post-surgery, all groups showed a significant increase in muscle strength in comparison to 3 months post-surgery. However, the BFR-group exclusively achieves additional improvements in muscle mass and strength to baseline values already 6-month after surgery (**Table 3**, **6**). Whereas no significant change in muscle mass and strength to baseline for the AC group was revealed, CON showed significant decreased outcomes after 6 months (**Table 3** and **6**). These findings are well in line with previous literature, illustrating persistent reductions in muscle mass and strength post TKA for patients without prehabilitation (Bade et al., 2010). Our results suggest that prehabilitation with BFRE enables patients to recover postoperative muscular deficits faster than control groups and were able to improve skeletal muscle mass, strength and disbalances to the contralateral leg within the first 6 months postoperatively. This result stands in contrast to previous prehabilitation concepts, which showed only a minor impact on postoperative rehabilitation (Moyer et al., 2017).

LIMITATIONS

The following limitations should be considered when interpreting our findings. Firstly, the methodology of measuring muscle mass by extremity circumference used in this study should be considered as an index of change in muscle size. Since these kinds of measurements includes soft-, adipose- connective- and muscle-tissue, only an estimation of the muscle mass and its change in the course of the study can be done. Future studies should use more valid methods of muscle mass calculation, such as body composition analysis by DXA measurements or MRI scans. Secondly, a possible interference in our results could be caused by a missing matching of the groups to baseline characteristics such as level of physical activity, preoperative muscular deficits, or leg-dominance. Thirdly, there is a possible risk of attention bias, as prehabilitation groups had more visitations to supervisors through the weekly training than the CON, which may have influenced the results preoperatively. Fourthly, level of activity and intensity of activity of the patients after the surgery was not recorded. Future studies should try to monitor postoperative patient activity to get valid data about the effects of prehabilitation on postoperative daily activity.

CONCLUSION

The present study is the first one describing the supporting impact of BFRE on skeletal muscle mass, strength, subjective pain perception and QoL pre-as well as post-TKA surgery. BFR prehabilitation appears to be a safe, patient compliant, easy-to-perform and effective tool to improve pre-as well as postoperative clinical outcomes and patient satisfaction in TKA. In a highly standardized clinical intervention such as TKA, BFR prehabilitation allows to prepare the patient physical capacities in the best possible way for surgery. Furthermore, in contrast to previous findings, the present

study shows that prehabilitation with BFR is able to support rehabilitation after primary TKA in a "better in, better out"-manner.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Comittee of the University Hospital Dusseldorf, Moorenstraße 5, 40223 Düsseldorf. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AF was responsible for study conception, conduction, evaluation and manuscript preparation. SJ collected and interpretated the data and was involved in the realization of the study. BB and CZ collected and interpretated the clinical data and were involved in the realization of the study. SJ and MB were responsible for statistical analyzation of the obtained data and writing the manuscript. All authors read and approved the final manuscript.

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Current Trends in Blood Flow Restriction

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Purpose: The purpose of the study was to explore how individuals in the United States of America applied BFR/KAATSU devices and administered BFR/KAATSU training. In addition, the study sought to examine safety topics related to BFR/KAATSU training.

Methods: The study was completed using survey research. Subjects were recruited through Facebook, email, and word of mouth. The survey was developed, piloted, and finally deployed March 22, 2021-April 21, 2021.

Results: In total, 148 consented to the research; 108 completed the survey, and of those 108, 70 indicated current use with BFR/KAATSU equipment. Professions represented included athletic training, personal training, physical therapy, and strength and conditioning. Among those currently using BFR/KAATSU training (n = 70), the following results were found. The most common devices used were inflatable devices (n = 43, 61.4%). Education completed prior to device administration was formal (n = 39, 55.7%) and/or self-directed (n = 37, 52.9%). Barriers were faced by 29 (41.4%) when trying to enact training. Techniques and parameters varied during application. Screening processes were used (n = 50, 71.4%) prior to training. The devices were used to determine restrictive pressure (n = 31, 44.3%), and a supine position was used most when determining initial restrictive pressure (n = 33, 47.1%). For subsequent restrictive pressure measurements, respondents repeated the same method used initially (n = 38, 54.3%). Workload was often defined as the length of time under tension/load (n = 22, 31.4%) and exercise was directly supervised (n = 52, 74.3%). Adverse effects included bruising, lightheadedness, and cramping (n = 15, 21.4%). The devices have also been applied on those with pathology (n = 16, 22.9%).

Conclusion: Those using blood flow restriction/KAATSU devices came from several professions and used an assortment of devices for BFR/KAATSU training. Individuals applied devices using a variety of parameters on populations for which efficacy has and has not been well defined.

Keywords: blood flow restriction, BFR training, kaatsu training, application, safety

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INTRODUCTION

Blood flow restriction (BFR) training involves the application of a device to an extremity to modify blood flow and may include brief and partial limitations in blood flow during exercise (Mouser et al., 2017; Mills et al., 2021). The pressure applied by the device is intended to limit arterial blood flow to a limb while fully restricting venous outflow in working muscles during exercise (Scott et al., 2015; Patterson et al., 2019). Devices used to alter blood flow vary in style. Patterson and Brandner (2018) identified types of devices which are commonly used to facilitate BFR training including KAATSU devices, knee wraps, inflatable devices, and the use of elastic tourniquets.

The KAATSU training device was the original blood flow training device. KAATSU training received a patent in the 1990s in the United States of America (Sato, 2005), and Yasuda et al. (2017) described KAATSU training devices as belts which facilitate blood pooling. Knee wraps have been described in the literature by authors as elastic in nature (Wilson et al., 2013; Head et al., 2015) and as wraps used for power lifting purposes (Luebbers et al., 2014; Luebbers et al., 2019). Loenneke and Pujol (2009) described the use of knee wraps as a form of practical occlusion (practical BFR). Inflatable devices are cuffs applied to the limb that can be inflated through an automatic device or handheld pump. Within the literature, terms such as a pressure cuff (Byrk et al., 2016) may be seen as opposed to inflatable devices or inflatable pumps. Tourniquets are air powered devices that apply pressure to a limb reducing or occluding circulation to a body part. The devices consist of an inflatable cuff, a unit which regulates pressure, and tubing which connects the cuff to the regulating unit (FDA, 2020).

Regardless of the style of device, the devices are applied proximally along a limb with minimal pressure to facilitate restriction (McEwen et al., 2019). Pressure affects blood flow in a nonlinear fashion within the brachial artery (Mouser et al., 2017), and superficial femoral artery (Crossley et al., 2019) and restriction pressures can be determined through a variety of means. Methods used to find restriction pressure include doppler ultrasound (Masri et al., 2016), the device itself (McEwan et al., 2019), subjective rating scales (Wilson et al., 2013), or capillary refill time (Freitas et al., 2021). Factors influencing the process of arterial blood restriction include the cuff's construction and dimensions, the site of restriction, individual attributes, and individual physiology (McEwen et al., 2019; Patterson et al., 2019) such as limb circumference (Loenneke et al., 2012; Jessee et al., 2016; Sieljacks et al., 2018) and diastolic blood pressure (Loenneke et al., 2012; Sieljacks et al., 2018).

Once the device has been applied, BFR/KAATSU training can be used in conjunction with a variety of exercise techniques. Methods of exercise used with BFR/KAATSU training devices include aerobic exercise (Pattterson & Brandner, 2018; Patterson et al., 2019; Formiga et al., 2020) and resistance exercise (Hughes et al., 2017; Wilk et al., 2018; Patterson et al., 2019). One recommendation for walking or cycling with BFR has been established by Patterson et al. (2019) and includes exercising two to three times per week at less than 50% heart rate reserve, VO_2 Max, for 5–20 min at 40–80% arterial occlusion pressure. Implementation of BFR with aerobic exercise in populations across the lifespan yielded improvements in function (Paton et al., 2017; Chen et al., 2019; Formiga et al., 2020). The use of low load resistance exercise with BFR to gain muscle strength and hypertrophy has just one of the following suggestions for use: two-four times per week using 75 repetitions (30-15-15-15) or repetitions to failure (Patterson et al., 2019). When applied with resistance training, BFR in conjunction with low load exercise was also effective at improving muscle strength and hypertrophy (Pearson & Hussain, 2015; Cook et al., 2017; Lixandrão et al., 2018).

Currently, little is known regarding how individuals are using different types of BFR/KAATSU training devices in the United States of America. The authors of three observational studies looked at experiences with BFR/KAATSU training (Nakajima et al., 2006; Yasuda et al., 2017; Patterson & Brandner, 2018). Patterson and Brandner (2018) assessed the use of BFR training globally by physicians, strength and conditioning specialists, rehabilitation specialists, sport specific scientists, personal trainers, and researchers. Authors of the remaining studies focused on the use and safety related to the KAATSU training (Nakajima et al., 2006; Yasuda et al., 2017). This study adds to the existing body of literature through its exploration of how BFR/KAATSU was being administered. Understanding how different forms of BFR/KAATSU training devices were being used can expose gaps in the literature needing further exploration. In addition, information concerning adverse effects could facilitate additional precautions when using different devices for BFR/KAATSU training. Therefore, the purpose of this study was to explore how individuals across different professions administered and used various forms of BFR/KAATSU training devices in the United States of America. In addition, the study sought to explore safety topics related to BFR/KAATSU training with various devices.

MATERIALS AND METHODS

The survey-based research study took place March 22, 2021-April 21, 2021. Prior to starting participant recruitment, the study was approved through the appropriate Institutional Review Board.

Participants

Those using BFR/KAATSU training devices were included in the study. To be included in the study, participants met the following criteria: 1) English speaking, 2) older than 18 years old, and 3) use BFR/KAATSU training for aerobic exercise, strength training exercise, or rehabilitation purposes in the United States. Subjects were excluded if 1) BFR/KAATSU training was not being used with patients/clients/athletes.

Data Collection

Data collection was completed in Qualtrics (Version XM), exported into Microsoft Excel (Version 2101) then the statistical software management system, IBM SPSS Statistics for Windows (Version 27).

Instrumentation

The survey was developed following a review of previous survey-based literature (Nakajima et al., 2006; Yasuda et al., 2017; Patterson & Brandner, 2018). Conversation among research team led to the development of topic areas, and the subsequent research questions were developed by one research member. Remaining research team members and an additional external contact reviewed questions for clarity and ease of read. A test pilot of the survey was administered in November 2020. A content expert recruited subjects and served as a liaison between the researcher and the subjects taking the pilot survey to ensure anonymity. The survey was restrictively administered to a group of 10 subjects on two separate occasions, one week apart. All 10 participants of the test pilot completed the survey the first time while eight participants completed the test pilot survey the second time. Data was analyzed using IBM SPSS Statistics for Windows (Version 24). Participants from the test pilot were all Caucasian with 60% of subjects identifying as male and 40% identifying as females. All were from the Midwest with a mean age between 31 and 40 years. Participants from the test pilot represented the professions of athletic training, physical therapy, and strength and conditioning with an average time in their respective fields of less than 10 years.

The survey test pilot took participants approximately 13 min to complete. The purpose of the test pilot was to assess the content presented in the survey. Normality of the data was assessed using the Shapiro Wilks test. Subsequent Pearson correlation and Spearman Rho correlation showed significance between measures with an alpha value of $p < 0.05$. Constructs with correlations display moderate correlation to high correlation. Cronbach's alpha on 24 applicable items was $\alpha = 0.484$. Considering the statistical results in conjunction with subject feedback, fifteen questions were modified or deleted. The final survey contained 37 questions.

Procedures

Recruitment was completed through convenience and snowball sampling through Facebook and email. The following groups agreed to be a part of sampling on Facebook: Kansas City Athletic Trainers Society; Women in Athletic Training Group; and the following National Strength and Conditioning Association (NSCA) Special Interest Groups: College Coaches, Personal Trainers, Sport Science and Performance Technology, and Sports Medicine/Rehabilitation. The following groups agreed to be surveyed through email: Collegiate Strength and Conditioning Association.

The survey was available for four weeks. All subjects completed the same survey, which was developed, housed, and deployed through Qualtrics. Participants were asked up to but no more than 37 questions divided into the following sections: Informed Consent, Product Use, Current Use, Safety, Demographics of patients, clients, and athletes, and Demographics of the respondent. The Informed Consent portion of the survey housed the informed consent documentation and asked participants to consent to the research. The questions within Product Use focused on the types of BFR/KAATSU training devices both previously and currently being used by the subject. The Current Use section asked questions pertaining to the methods used to apply BFR/KAATSU training. The Safety section assessed safety related concerns and adverse effects seen when using BFR/KAATSU training devices. The final two sets of questions asked about demographics of the patients/clients/athletes for which BFR/KAATSU training was applied and the demographics of the individual completing the survey. A subject could terminate participation in the survey at any given time by closing out of the survey. At the conclusion of the survey, participants were offered the opportunity to enroll for a chance to win one of five $10 gift cards.

RESULTS

Study Response Rates

The survey yielded 149 responses; 148 individuals consented to participate in the survey research. Of those consenting to the survey research, there were 40 (27%) individuals who did not complete the survey, 38 (25.7%) who were not currently using BFR/KAATSU training, and 70 (47.3%) who at the time of the survey were using BFR/KAATSU training.

Previous BFR/KAATSU Training Use

Information regarding those previously using BFR/KAATSU training devices ($n = 108$) and those currently using BFR/KAATSU training devices ($n = 70$) can be found in **Table 1**. Individuals who were not actively administering BFR/KAATSU training ($n = 38$, 35.2%) were henceforth excluded. Reasons identified for no longer using BFR/KAATSU training were as follows: "I previously utilized for injury rehabilitation, is no longer necessary", "not allowed per company because I have not taken company's training", "I am at a different school where we do not have blood flow restriction devices", and "I do not have the resources in my athletic training room to use this form of rehab".

Current BFR/KAATSU Training Use

The remaining respondents ($n = 70$) identified themselves as males ($n = 41$, 58.6%) and females ($n = 29$, 41.4%). Additional information on demographics and professional careers can be found in **Table 2**.

Education

Respondents suggested obtaining both formal education ($n = 39$, 55.7%) and self-education ($n = 37$, 52.9%) for their respective BFR/KAATSU devices. Of those who received formal training, 29 (74.4%) felt their training promoted a singular device, and 24 (61.5%) indicated their education was tailored toward a specific device. The majority ($n = 58$, 82.9%) felt that some sort of education should take place prior to BFR/KAATSU training implementation, while five felt education prior to implementation was not needed and an additional seven had no opinion on the matter.

TABLE 1 | Previously and currently used devices as indicated by respondents.

Type of Device	Previously Used	Currently Used	Currently Used Devices Identified
Elastic tourniquet device	*n* = 21	*n* = 9	3M (*n* = 1) BFR Bands (*n* = 1) Generic brand (*n* = 1) HMKL (*n* = 1) Koala Bands (*n* = 1) Konmed/OBM (*n* = 1) Defi PTS-PBFR (*n* = 1)
Inflatable device	*n* = 47	*n* = 43	Air Bands (*n* = 4) Mad-Up (*n* = 2) Occlusion Cuffs (*n* = 1) Edge Rehab Cuffs (*n* = 2) Smart Cuffs (n = 10) B Strong (*n* = 7) Defi PTS-PBFR (*n* = 16) Fitcuffs (n = 2) H + Cuffs (n = 2) BFR Signature Series (*n* = 1) BFR Occlude (*n* = 1) Throwraft original TD 2401 (Note: this is a personal floatation device) (*n* = 1) VALD (n = 2) Unknown name (*n* = 2)
KAATSU training device	*n* = 11	*n* = 9	Air Cuffs (*n* = 1) Dumbbell pressure exercise (*n* = 1) Inflatable Cuffs (*n* = 1) KAASTU Cycle Pro (*n* = 1) Nano (*n* = 2)
Knee wraps	*n* = 11	*n* = 2	LP Sports Protector (*n* = 1)
Other	*n* = 8 BFR Bands (*n* = 1) KELVI BFR (*n* = 1) RockCuff (*n* = 1) DELFI-PTS-PBFR (*n* = 5)	*n* = 7	Ace bandages (*n* = 1) Delfi PTS-PBFR (*n* = 3) KELVI (*n* = 1) Rock Cuff (*n* = 1)

TABLE 2 | Demographics.

Demographics of Respondents	
Gender	Male (*n* = 41) Female (*n* = 29)
Age (in years)	18–30 (*n* = 36) 31–40 (*n* = 27) 41–50 (*n* = 5) 51–60 (*n* = 1) 61 and older (*n* = 1)
Ethnicity	White (*n* = 57) Black, African American (*n* = 3) Asian (n = 1) White/Black, African American (n = 1) American Indian or Alaskan Native (*n* = 4) Asian/Native Hawaiian or Pacific Islander (*n* = 1) Hispanic or Latino/a (*n* = 1) White/Hispanic or Latino/a (*n* = 1) All race (*n* = 1)
Location	Northeast (*n* = 11) Southeast (n = 17) Midwest (*n* = 27) West (*n* = 7) Southwest (*n* = 7) Unanswered (n = 1)
Profession	Athletic Training (*n* = 33) Personal Training (*n* = 6) Physical Therapy (*n* = 19) Physical Therapy Aide (n = 3) Strength and Conditioning (*n* = 20) Other Athletic Training Student (*n* = 1) Lecturer of Exercise Science (n = 1) Occupational Therapy (*n* = 1) Semi-retired Consultant (n = 1)
Years in Profession	1–10 years (*n* = 50) 11–20 years (*n* = 18) 21–30 years (*n* = 1) 31 or more years (*n* = 1)

Implementation

Barriers

Barriers were faced by 29 (41.4%) when trying to implement BFR/KAATSU training into practice. Barriers noted by those facing barriers included the cost of equipment (*n* = 20, 69%), lack of training (*n* = 10, 34.5%), doubts of effectiveness (*n* = 9, 31%), and a lack of clinical efficacy (*n* = 4, 13.8%). Other barriers noted were "concerns about medical complications (e.g., DVTs [Deep Vein Thrombosis])", "concerns of medical staff", "confidence in applying technique and having patient/client understand that BFR training is hard", "lack of physician/surgeon buy-in", "patient consent", "patient fear", "patients being willing to try it", and "supervisor approval".

Screening

Screening processes facilitated by respondents were comprised of medical screening forms including risk assessments and/or in person physical examinations (*n* = 27, 38.6%), both waiver/release forms and medical screening forms including risk assessments and/or in person physical examinations (*n* = 22, 31.4%), waivers/release forms (*n* = 1, 1.4%), and other screening processes (*n* = 2, 2.9%): "assure pt [patient] has no contraindication to BFR per a list and acquire consent from patient after describing treatment", and "screening is done based off of recommendations of Owens Recovery Science". Additionally, 57 (81.4%) respondents considered the psychosocial aspects related to BFR/KAATSU training. Eighteen (25.7%) did not conduct screening. Reasons suggested for a lack of screening were: "all participants are screened by medical department prior to contact with us", "they are cleared by ATs[Athletic Trainers] for physical activity our requisites are met", "initial health screening showed no signs of potential adverse interactions", "we already know based on the medical history/chart if they are able to use this or not", "communication with AT to determine if they are a good candidate for modality of BFR", "we ask if they have history of blood clots", "verbal consent", "elite athletes", "it is safe to use on the athletic population and patients I use it on", "only self-use", "I have only used on myself", "use only on myself", and "we just don't have one outside of the one they sign for therapy".

Application

Survey responses suggested the following methods to determine restrictive pressure: the use of comfort (i.e., "7/10" perceived tightness) (*n* = 13, 18.6%), limb circumference (*n* = 4, 5.7%), standard blood pressure (*n* = 5, 7.1%), doppler ultrasound (*n* = 11, 15.7%), or the device was set to determine restrictive pressure (*n* = 31, 44.3%). The remaining six responses (8.6%) provided other methods to determine restrictive pressures: "systolic pressure x 1.5", "comfort and blood pressure", "skin color, there should be a faint pulse, color should return to skin when pressed", "capillary refill with progressive tightness based on both

TABLE 3 | Exercise employed with BFR/KAATSU training.

Types of Exercises Used with BFR/KAATSU Training	Number of Respondents Using This Form of Exercise (n =)
Single Joint Exercise	51
Single Joint Machine Based Exercise	37
Single Joint Free Weight Exercise	47
Multi Joint Exercise	57
Multi Joint Machine Based Exercise	32
Multi Joint Free Weight Exercise	49
Cycling	29
Walking	15
Jogging	10
Swimming	4
Rowing	1
Other	1
Recumbent stepper	—
Sport Specific	—

refill and feedback", "device, will often lower pressure for first session", and "not able to use any equipment".

The majority (n = 67, 95.7%) believed personalizing restrictive pressure would reduce adverse effects, and multiple positions were used to determine restrictive pressure. Restrictive pressure determination was completed with the patient/client/athlete in a supine position (n = 33, 47.1%), seated position (n = 11, 15.7%), standing position (n = 9, 12.9%), and in an exercise dependent position (n = 17, 24.3%). For subsequent exercises, restrictive pressure was determined by the same measures as the initial assessment (n = 38, 54.3%), a different method from the initial method based on exercise position (n = 11, 15.7%), or no additional measurement of restriction pressure was made for subsequent exercises (n = 21, 30%). Workload was determined using heart rate (n = 5, 7.1%), percentage of 1 RM (n = 18, 25.7%), length of time under tension/load (n = 22, 31.4%), work to failure (n = 14, 20%), and other methods (n = 11, 15.7%). Other methods suggested were "using Delfi protocol, adding resistance if not worked to failure by end of protocol at next session", "both %1 RM and length of time under tension", "load and reps", "low weight, high rep, 15–20 min", "30/15/15/15", "prescribed reps/sets from educational training", "reps in deserve [sic], muscle fatigue scale", "perceived exertion", "RPE, by feel", "muscle groups worked", and "unknown".

Blood flow restriction and KAATSU devices were applied for various lengths of time. Devices provided restriction for the duration of the workout (n = 24, 34.3%), devices were loosened or released between exercises (n = 29, 41.4%), devices were loosened or released between sets of an exercise (n = 10, 14.3%), or through other methods (n = 5, 7.1%); two individuals did not respond to the question. Other methods described by respondents were "as tolerated for prescribed exercise", "client dependent-either intermittent or continuous", "client dependent", "provide restriction for duration up to 8 min max", and "unknown". The majority of respondents provided direct supervision to the patient/client/athlete while BFR/KAATSU training was being administered (n = 52, 74.3%). Additional respondents provided some supervision to the patient/client/athlete while BFR/KAATSU training was being administered (n = 14, 20%), while others provided no supervision to the patient/client/athlete while BFR/KAATSU training was being administered (n = 4, 5.7%).

Patients/clients/athletes received BFR/KAATSU training on the upper extremity (n = 4, 5.7%), lower extremity (n = 18, 25.7%), or both the upper extremity and lower extremities (n = 48, 68.6%). Activities for which BFR/KAATSU training were administered included strength training exercises (n = 47, 67.1%), aerobic exercise (n = 15, 21.4%), rehabilitation exercises (n = 57, 81.4%), and other activities (n = 5, 7.1%). Activities described were "active recovery", "effects of BFR on sprint time", "healing", "I know PT's [Physical Therapists] use it for rapid rehab after surgery", and "recovery". Specific forms of exercises performed with BFR/KAATSU can be seen in **Table 3**. Blood flow restriction and KAATSU training were administered: 1-2 sessions per week (n = 51, 72.9%), 3-4 sessions per week (n = 18, 25.7%), and 5-6 sessions per week (n = 1, 1.4%) but not 7 or more sessions per week (n = 0, 0%).

Patient Demographics and Safety

The demographics of those for whom BFR/KAATSU training was applied can be seen in **Table 4**. Regarding safety, BFR/KAATSU training was administered on patients/clients/athletes with pathology by 16 (22.9%) respondents. Pathologies noted by respondents for which they have applied BFR/KAATSU training were hypertension, diabetes, obesity, EDS [Ehlers Danlos Syndrome], osteopenia, and unspecified cardiac conditions. Adverse effects from the administration of BFR/KAATSU training were seen by 15 (21.4%) respondents. Adverse effects seen can be seen in **Table 5**. Those who discontinued the use of BFR/KAATSU training did so for a variety of reasons presented in **Table 6**.

DISCUSSION

Administration and Use of Various Forms of BFR/KAATSU Training Devices

The main finding of the research was the diversity in the selection and application of BFR. A variety of devices have been used in the facilitation of BFR/KAATSU training. The most common type of device applied was the inflatable device (43.5%, n = 47) followed by elastic tourniquet-based devices (19.4%, n = 21). Respondents reported equal use of KAATSU devices and knee wraps. Results of the current study were similar to a previous study by Patterson and Brandner (2018) where the use of inflatable devices, KAATSU devices, and knee wraps were comparable. One area that differed between the present study and Patterson and Bradner (2018) was the use of elastic tourniquet-based devices. While the present study found 19.4% of respondents (n = 108) have used an elastic tourniquet-based device, Patterson and Brandner (2018) found only 3.6% of respondents (n = 115) have used an elastic tourniquet-based device. Terminology used to describe the devices was based on Patterson and Brandner (2018) and may not reflect how respondents describe their

TABLE 4 | Demographics.

Demographics of Those for which BFR was Applied to	
Gender	Male (*n* = 64, 91.4%) Female (*n* = 48, 68.57%) Gender Non-Conforming (*n* = 2, 2.9%) Transgender (*n* = 3, 4.3%) Gender unknown (*n* = 1, 1.4%)
Age (in years)	Under 20 (*n* = 45, 64.3%) 21–30 (*n* = 58, 82.9%) 31–40 (*n* = 31, 44.3%) 41–50 (*n* = 20, 28.6%) 51–60 (*n* = 12, 17.1%) 61 and older (*n* = 6, 8.6%)
Ethnicity	White (*n* = 61, 87.1%) Black, African American (*n* = 42, 60%) Asian (*n* = 16, 22.9%) Pacific Islander, Hawaiian (*n* = 10, 14.3%) Hispanic or Latino/a (*n* = 27, 38.6%) Native American or Alaskan Native (*n* = 11, 15.7%) Multi-racial (*n* = 1, 1.4%) Unknown ethnicity (*n* = 1, 1.4%)

TABLE 5 | Adverse reactions described by respondents.

Described Demographics	Adverse Outcome	Other Noted Factors	Device Used	Screening Procedure
Elderly Age: 70s	Bruising, petechiae	—	Not enough info to determine device used; several devices indicated for current use	Waiver/Release and medical screening
Bodybuilding athlete Age: 40s	Bruising, petechiae	—	Not enough info to determine device used; several devices indicated for current use	Waiver/Release and medical screening
Male Age: 18–25	Giddy	—	Not enough info to determine device used; several devices indicated for current use	Medical screening
Caucasian female Age: 18–21	Lightheaded, increased body temperature	—	KELVI	Medical Screening
Athlete Age: college	Dizzy, lightheaded	Did not eat prior	Ace Bandage	No Screening
Caucasian female Age: mid 60s	Elevated heart rate, sweating, shortness of breath	—	Smart Cuffs	Waiver/Release and medical screening
Male Age: 40s	Increased pain with cuff occlusion	—	Delfi PTS-PBFR	Consent, ask contraindications
Unknown	Lightheadedness, muscle cramping	—	Delfi PTS-PBFR	Waiver/Release and medical screening
Hispanic Female Age: 21	Nausea, vomiting	—	Delfi PTS-PBFR	Waiver/Release and medical screening
Athletes High school, college Varied gender and race	Moderate cramping, lightheadedness, or did not tolerate sensation	—	Delfi PTS-PBFR	ORS specified

devices, particularly tourniquet-based devices. Other terminology, including pneumatic tourniquet, has been used when describing tourniquet-based devices (McEwen et al., 2019; Patterson et al., 2019).

Among those administering BFR/KAATSU training at the time of the survey, respondants likewise employed a variety of devices.The most frequently applied device was still the inflatable device. This finding again mirrored Patterson and Brandner (2018) as handheld inflatable devices and automatic inflatable devices were reported as the most used devices.

At the time of the study, BFR/KAATSU training was being administered by those identifying as male/female genders across the country. Most predominantly, those administering BFR/KAATSU training were from a younger population (18–40 years old and practicing less than 20 years) and represented a variety of professions including athletic training, occupational therapy, physical therapy, personal training, and strength and conditioning. In previous survey-based research, authors have likewise noted administration by those of male and female genders (Nakajima et al., 2006; Yasuda et al., 2017; Patterson & Brandner, 2018; Mills et al., 2021), and administration by a younger demographic (Patterson & Brandner, 2018; Mills et al., 2021) across a variety of professions (Patterson & Brandner, 2018).

The present study also found 35.18% (*n* = 38) of individuals no longer administering BFR/KAATSU training. Minimal additional data was provided justifying discontinuation. Reasons that were cited included facility resources and facility policy on training prior to use of BFR/KAATSU training. While no additional literature could be found regarding those who have discontinued the use of BFR/KATTSU training, Mills et al. (2021) noted barriers among those who have never used BFR training included a lack of certification, training, and resources which mirrors concerns noted in the present study regarding facility policy and resources for BFR/KAATSU training use. Relative to discontinued use of BFR training, others have noted side effects or adverse reactions (Nakajima et al., 2006; Yasuda et al., 2017; Patterson and Brandner, 2018) could lead to temporary or permanent discontinuation of training. Side effects seen among those who were currently using devices can be found later in the discussion section.

Few researchers have assessed barriers implementing BFR/KAATSU training *via* survey research. In the present study, barriers were experienced by participants when implementing

TABLE 6 | Reasons respondents discontinued BFR/KAATSU training.

Non Safety Related	Safety Related	Other
Heavy load strength training is able to be performed consistently	Client was found to have developed a blood clot issue	Dangerous actions for people with poor health
It is used with our Physical Therapists and Sports Medicine Staffs in our settings. We have not incorporated in team/individual training, only utilize for personal use	Discomfort, Fatigue	Over time, a blood clot can develop that can lead to a fatal pulmonary embolism
I want to do it another way	Some tired, occasionally need a short rest	—
Money	Discomfort, had a patient who had fear of blood pressure cuffs but never told therapist, increased paraesthesia in the limb	—
N/A	Excessive pain, discomfort, or noticeable swelling	—
Progression to higher intensities due to rehab progress	Pain due to too much restriction	—
Time restrictions	Exercise pursor [sic] reflex symptoms	—
Time under pressure was reached	Extreme discomfort and loss of touch sensation	—
Wasn't anything special	Failure or too uncomfortable for patient	—
When the patient reaches 15–20 min time of BFR cuff placed on leg or arm	Feeling much discomfort while exercising	—
Work reasons	Only use for 10–15 min	—
	If athlete complains of severe and unusual discomfort	—
	If the person cannot handle the pressure or repeatedly cannot hit target range	—
	Improper operation caused by bump	—
	Patient discomfort	—
	Patient discomfort, significant DOMS	—
	Perceived exertion gets too high or significant fatigue or muscle failure	—
	Prescreen, but if I find later that the person has a history of clotting I will discontinue	—
	Unable to tolerate the cuff, fatigue, inability to complete repetition range without severe compensatory patterns of movement	—
	Vomiting, lightheadedness	—

TABLE 7 | Actual device type.

Type of Device	Device Name
Tourniquet device	Delfi PTS-PBFR
Inflatable device	AirBands BFR Bands-Signature Series B Strong Fit Cuffs H + Cuffs MAD- UP Occlusion CuffSmart Cuffs The EDGE Restriction Systems VALD
KAATSU Training device	KAATSU Cycle 2.0 KAATSU Nano
Wraps	BFR Bands Koala Bands Rock Cuff
Other	3M ACE bandage Conmed/OBM HMKL KELVI (Cryo/Thermotherapy Device) LP Sports Protector Throwraft Original TD2401 (Personal Flotation Device)

BFR/KAATSU training. The most frequently cited barrier was the cost of the apparatuses followed by a lack of training. While not assessed through the study, it can be noted that the most frequently cited devices (**Table 1** and **Table 7**) have device specific training which can add to the potential cost for the user. Mills et al. (2021) found barriers to BFR implementation likewise included a lack of information, certification, and resources. In addition to the cost and training, some faced barriers on the effectiveness of BFR/KAATSU training, as well as concerns by overseeing medical practitioners or supervisors, and the patients/clients/athletes for which BFR/KAATSU training was being administered. Rolnick et al. (2021) identified screening safety, selecting an appropriate training pressure, device selection, and the influence of perceptual demands on compliance as barriers to BFR use. These factors likewise showed variability throughout the present study and may present barriers in the administration of BFR/KAATSU training.

The majority of respondents (82.9%, $n = 58$) believe training prior to BFR/KAATSU implementation should take place. While no additional information could be found regarding perceptions of BFR/KAATSU training implementation, respondents of this survey indicated training was necessitated by the BFR/KAATSU device company or the facilities where one is employed. Education received by respondents was both formal and self-facilitated but not all training promoted a singular device or was tailored toward a specific device. It is unknown how education was disseminated among the respondents of this survey.

Nearly three-quarters of respondents indicated conducting some sort of screening process and just over 80% considered

the psychosocial aspects of BFR/KAATSU training. The most predominantly facilitated process was a medical screening or a medical screening and a waiver with the patient/client/athlete prior to use. Yasuda et al. (2017) also found most respondents performed interviews or assessments prior to application of KAATSU training either the first time or every time the device was applied. The present study also revealed 25.7% of respondents had no screening process. Upon further examination there were indications a screening process took place at some point. Comments on the open-ended question included reference to screenings by other departments and use of initial health screenings.

The same open-ended question suggested some screened on a limited basis or not at all. Those that assessed patients/clients/athletes on a limited basis suggested inquiring about blood clot history, while others asked for verbal consent. Also noted in the comments was the perception that no screening was needed when applying BFR/KAATSU training on those who were perceived as healthy. Patterson and Brander (2018) saw similar comments in which respondents felt there were no contraindications in populations of individuals who may be healthy, young, or athletic. In reviews of healthy populations, low intensity exercise with blood flow restriction has shown effects on hemodynamics within a normal spectrum (Neto et al., 2017) and improved strength gains and muscle mass greater than low intensity exercise alone (Slysz et al., 2016). Furthermore, stroke volume, blood pressure, heart rate, fibrinolytic potential, coagulation activity, and post occlusion blood flow responded the same as free flow high load resistance exercise in short term studies (Loenneke et al., 2011). Additionally, Patterson et al. (2019) suggested when applied and performed appropriately BFR should not produce muscle damage unless other susceptibility to adverse physiologic effects exist. For all populations, correct application and safety in training are important (Sato, 2005; Loenneke et al., 2011; Hughes et al., 2017; Patterson et al., 2019). Regardless, for those wanting to implement a screening tool, Kacin et al. (2015) created a screening questionnaire and Rolnick et al. (2021) proposed a funnel approach which can aid health professionals in determining if the treatment is appropriate.

The present study found 95.7% of those administering BFR/KAATSU training believed personalized restrictive pressure was needed to prevent adverse effects. There was variability in the procedures used to determine restrictive pressure. Techniques to determine restrictive pressure included the use of doppler ultrasounds, the device themselves, subjective rating scales and the use of capillary refill time. When administering BFR/KAATSU training, methods to obtain the pressure vary. For instance, the application of doppler ultrasound has shown reproducibility (Bezerra de Morais et al., 2017) and both the doppler ultrasound (Masri et al., 2016) and devices set to determine limb occlusion pressure (McEwan et al., 2019) have been advocated. For those unable to afford/operate doppler ultrasound, pulse oximeters have shown potential in determining occlusion pressure within the upper extremity (Zeng et al., 2019; Lima-Soares et al., 2020). Subjective rating scales can also be conducted with devices for which pressure cannot be determined through conventional means (Wilson et al., 2013); however, some have noted concerns with reliability of the use of the subjective rating scale to determine limb occlusion pressure (Bell et al., 2020). Additional procedures performed by respondents of the present study related to the use of skin color, pulse, and capillary refill time. Within the current study, 24.3% (n = 17) determined restrictive pressure in an exercise dependent position with 15.7% (n = 11) determining restrictive pressures for subsequent exercises using methods based on the exercise position. Sieljacks et al. (2018) and Hughes et al. (2018) demonstrated body position does influence arterial occlusion pressure in lower extremity exercise.

In this investigation, responses related to the administration of BFR/KAATSU training both matched (Nakajima et al., 2006; Patterson & Brandner, 2018; Patterson et al., 2019) and conflicted (Patterson & Brandner, 2018) with previous authors. Frequency of use was one similar area. In this study training methods were most applied 1–2 times per week (72.9%, n = 51) or 3-4 sessions per week (25.7%, n = 18). Authors have suggested BFR/KAATSU training was most administered one to three sessions per week (Nakajima et al., 2006), or one to two sessions and three to four sessions per week (Patterson & Brandner, 2018). Patterson et al. (2019) suggested administering BFR two to three times per week. Types of exercise employed also presented similarly between the current study and research from previous authors. Patterson and Brandner (2018) found cycling and walking were the most frequent aerobic exercises used with BFR which was reflected in the current study. Workload was one area which differed. Patterson and Brandner (2018) found most respondents determined workload using percentage of a one repetition maximum (1RM) with the following repetitions: 30 -15-15-15, or the use of repetitions to failure while the current study found length of time under tension/load was more frequently used than a percentage of 1RM or work for failure. Like Patterson and Brandner (2018), the results of this investigation indicate great variability in administration.

Safety Topics Related to BFR/KAATSU Training With Various Devices

The second objective of the study was to explore safety related to the use of BFR/KAATSU training. The survey explored three areas related to safety. Safety topics addressed were the use of BFR/KAATSU training on individuals with pathology, adverse effects seen following device use, and reasons for discontinuing BFR/KAATSU training.

In the present study, 22.8% (n = 16) of respondents applied BFR/KAATSU training to those with pathology. Respondents indicated BFR/KAATSU training was most applied to individuals with obesity (37.5%, n = 6), hypertension (37.5%, n = 6), diabetes (25%, n = 4), and osteoporosis (12.5%, n = 1). Literature related to the use of BFR/KAATSU training with the four identified

pathologies was limited. Nakajima et al. (2006) and Yasuda et al. (2017) have found practitioners using KAATSU training among those with obesity, hypertension, and diabetes. Bond et al. (2017) has assessed the effects of BFR on individuals who are both sedentary and obese finding increases in 1 RM and post occlusion blood flow. Nascimento et al. (2019) suggested greater understanding of blood flow restriction's effect on coagulation would be beneficial for those at an increased risk of thrombi development including individuals with obesity, hypertension, and diabetes. Blood flow restriction has; however, shown positive hemodynamic effects (Loenneke et al., 2011; Neto et al., 2017; Yan et al., 2018; Nascimento et al., 2019) including among those with hypertension (Barili et al., 2018).

Specific to those who have diabetes, Kacin et al. (2015) indicated the potential risk of neurological injury caused by ischemia and nerve compression particularly among those with reduced peripheral nerve function. Few studies have explored the effects of administering BFR/KAATSU training on those with osteoporosis. Silva et al. (2015) found a small sample of women with osteoporosis were able to improve maximal dynamic strength on knee extension exercise and Yasuda et al. (2017) found practitioners using KAATSU training among individuals with osteoporosis.

For those uncertain how BFR/KAATSU training responds within a population or those with pathologies for which the efficacy of BFR/KAATSU training has not been ascertained, including the pathologies noted by respondents of the present study, some additional recommendations have been made. Nascimento et al. (2019) proposed an alternative exercise regime for resistance training using 50% of the 1 RM. In addition, Kacin et al. (2015) developed a screening tool and Rolnick et al. (2021) a funnel which may help in determining whether to administer BFR/KAATSU training. Finally, Patterson et al. (2018) suggested the use of clinical prediction rules to assess for additional risk particularly for venous thromboembolism.

Adverse effects were seen by those applying devices marketed for BFR/KAATSU training as well as those applying devices not marketed for BFR/KAATSU training. Details about adverse reactions can be seen in **Table 5**. With the exception of one adverse effect where prior food consumption was called into question, it is unknown if other personal factors influenced the adverse reaction. The adverse effects described in this investigation matched common reactions presented by other authors (Nakajima et al., 2006; Yasuda et al., 2017).

Individuals discontinued the use of BFR/KAATSU training due to changes to training, facility concerns, monetary issues, as well as safety. Reasons for discontinuation of BFR/KAATSU training (**Table 6**) directly related to side effects (e.g. lightheadedness and pain) were similar to side effects reported previously (Nakajima et al., 2006; Yasuda et al., 2017; Patterson and Brandner, 2018). Nascimento et al. (2019) recommended further research to quantify side effects to develop clearer parameters for use particularly among patients/clients/athletes who may have pathology or who may be older. Furthermore, quantifying a side effect versus an adverse reaction may limit ambiguity seen in the present study.

LIMITATIONS

There were limitations in the current study. The survey did not go through content validation nor were content validation coefficient statistical analysis completed following the development of the survey. A single test pilot was completed; however, additional revisions and analysis could have been completed to ensure its validity. Additionally, the survey was long at 37 questions taking an average of nearly 11 min to complete. Future investigations should explore survey constructs including verbiage for greater clarity.

The majority of the survey were selection-based questions. The questions potentially prevented respondents from elaborating or required a best fit answer which may not reflect what was actually being done. Participants were however, given the opportunity to provide written responses on several constructs. The written work likewise posed limitations. Some of the written work presented incomplete thoughts and typographical errors limiting the ability to interpret what was written.

Finally, COVID-19 pandemic was still taking place at the time of the survey. While there was some return daily life; it is unknown if the constraints of the pandemic precluded some participants from participating as he/she/they may have been unable to used BFR/KAATSU training based on their particular circumstances.

CONCLUSION

Overall, the study demonstrated diversity in the use of blood flow restriction. Devices used by participants varied in style and brand including those marketed and not marketed for BFR/KAATSU specific use. Barriers were seen by some when trying to implement BFR/KAATSU training. Formal training, self-training, or a combination of both were completed by most study participants. Many noted the inclusion of some sort of screening process prior to administering BFR/KAATSU training. The methodologies used to administer BFR/KAATSU training were vast. Adverse effects were seen by participants and BFR/KAATSU training was administered to those with pathology. Finally, discontinuation of BFR/KAATSU training occurred for reasons directly related to BFR/KAATSU training application and non-device related factors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

MC developed and administered the project including the development of the survey instrument and took primary lead

in writing manuscript. ES served as doctoral committee chair reviewing, guiding, and editing entire project. JN and AS served as content experts providing insight throughout project development and writing. JN served as liaison for survey test pilot. HSS served as a statistical analysis content expert and guided MC through the statistical analysis and representation of the statistics in writing.

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SUPPLEMENTARY MATERIAL

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SYSTEMATIC REVIEW
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Beneficial Role of Blood Flow Restriction Exercise in Heart Disease and Heart Failure Using the Muscle Hypothesis of Chronic Heart Failure and a Growing Literature

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Background: Blood flow restriction exercise (BFRE) has become a common method to increase skeletal muscle strength and hypertrophy for individuals with a variety of conditions. A substantial literature of BFRE in older adults exists in which significant gains in strength and functional performance have been observed without report of adverse events. Research examining the effects of BFRE in heart disease (HD) and heart failure (HF) appears to be increasing for which reason the Muscle Hypothesis of Chronic Heart Failure (MHCHF) will be used to fully elucidate the effects BFRE may have in patients with HD and HF highlighted in the MHCHF.

Methods: A comprehensive literature review was performed in PubMed and the Cochrane library through February 2022. Inclusion criteria were: 1) the study was original research conducted in human subjects older than 18 years of age and diagnosed with either HD or HF, 2) study participants performed BFRE, and 3) post-intervention outcome measures of cardiovascular function, physical performance, skeletal muscle function and structure, and/or systemic biomarkers were provided. Exclusion criteria included review articles and articles on viewpoints and opinions of BFRE, book chapters, theses, dissertations, and case study articles.

Results: Seven BFRE studies in HD and two BFRE studies in HF were found of which four of the HD and the two HF studies examined a variety of measures reflected within the MHCHF over a period of 8–24 weeks. No adverse events were reported in any of the studies and significant improvements in skeletal muscle strength, endurance, and work as well as cardiorespiratory performance, mitochondrial function, exercise tolerance, functional performance, immune humoral function, and possibly cardiac performance were observed in one or more of the reviewed studies.

Conclusion: In view of the above systematic review, BFRE has been performed safely with no report of adverse event in patients with a variety of different types of HD and in patients with HF. The components of the MHCHF that can be potentially improved with BFRE

include left ventricular dysfunction, inflammatory markers, inactivity, a catabolic state, skeletal and possibly respiratory muscle myopathy, dyspnea and fatigue, ANS activity, and peripheral blood flow. Furthermore, investigation of feasibility, acceptability, adherence, adverse effects, and symptoms during and after BFRE is needed since very few studies have examined these important issues comprehensively in patients with HD and HF.

Keywords: blood flow restriction, heart disease, heart failure, skeletal muscle, blood flow restricted exercise

INTRODUCTION

The "muscle hypothesis of chronic heart failure" (MHCHF) attributes the decreased exercise tolerance common in heart failure (HF) to skeletal muscle atrophy and metabolic inefficiency which stimulates a viscous cycle of dyspnea and fatigue; increased ventilation; sympathetic nervous system (SNS) excitation; increased afterload and reduced peripheral blood flow; and a catabolic state all of which worsen cardiac and skeletal muscle performance. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013). Many of the same factors likely contribute to exercise intolerance in heart disease (HD) despite the MHCHF being developed for HF. Many forms of HD elicit many of the factors described in the MHCHF falling within any stage of the HD continuum, but are often less extreme since HF is the end-stage of HD. In fact, HF is defined as a clinical syndrome with the most common characteristics being dyspnea, fatigue, abnormal ventricular filling, and elevated filling pressures resulting in the inability of the heart to pump blood to the body at a rate commensurate with its needs (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013).

Blood flow restriction exercise (BFRE) has become a common method to increase skeletal muscle strength and hypertrophy for patients with a variety of orthopedic and other musculoskeletal disorders in whom limited activity, exercise, and workloads are common. (Hughes et al., 2017; Van Cant et al., 2020; Nitzsche et al., 2021). A substantial literature of BFRE in older adults exists in which significant gains in strength and functional performance have been observed without report of adverse events. (Beckwée et al., 2019; Centner et al., 2019; Rodrigo-Mallorca et al., 2021; Labata-Lezaun et al., 2022). Sophisticated tourniquets exist which allow for a more precise and personalized reduction in blood flow based on the limb occlusion pressure enabling safer and more precise BFRE in older adults and in patients with HD and HF. (Weatherholt et al., 2019; Masri et al., 2020; Bordessa et al., 2021; Murray et al., 2021).

The reduction in blood flow and subsequent hypoxia within exercising skeletal muscle during BFRE stimulates anaerobic metabolism and metabolite accumulation promoting rapid muscular fatigue, up-regulated muscle protein synthesis, systemic anabolic hormone release, and possibly angiogenesis. (Loenneke et al., 2012; Pignanelli et al., 2021; May et al., 2022; Reina-Ruiz Á et al., 2022). However, BFR during exercise does elicit a greater increase in hemodynamic response which appears to be less during aerobic exercise compared to resistance training. (Pinto and Polito, 2016; Crisafulli et al., 2018; Pinto et al., 2018; Wong et al., 2018; Silva et al., 2019; Wong et al., 2021). Furthermore, the size of the muscle group appears to influence the hemodynamic response during BFRE with greater muscle groups eliciting a greater hemodynamic response. (Pinto and Polito, 2016; Crisafulli et al., 2018; Pinto et al., 2018; Wong et al., 2018; Silva et al., 2019; Wong et al., 2021). Factors such as mode of exercise, size of muscle group, and BFRE protocol in patients with HD and HF warrants further investigation in view of a limited, but growing literature.

One such BFRE protocol is cuff release after one or more sets of BFRE since there is potential to elicit favorable effects on skeletal muscle and the vasculature including an increase in nitric oxide and endothelium dependent vasodilation due to vascular sheer stress. (Pinto and Polito, 2016; May et al., 2017; Crisafulli et al., 2018; Pinto et al., 2018; Wong et al., 2018; Silva et al., 2019; Wong et al., 2021). In fact, cyclic occlusion and reperfusion via BFRE may promote favorable acute and chronic effects on cardiac and cardiovascular performance in hypertensive subjects and patients with HD and HF. (Shweiki et al., 1992; Higashi and Yoshizumi, 2004; Takano et al., 2005; Horiuchi and Okita, 2012; Pinto and Polito, 2016; May et al., 2017; Crisafulli et al., 2018; Pinto et al., 2018; Wong et al., 2018; Christiansen et al., 2019; Silva et al., 2019; Christiansen et al., 2020; Kambič, 2020; Liu et al., 2021; Wong et al., 2021; Li et al., 2022). Thus, personalized BFRE has the potential to improve skeletal muscle and cardiovascular performance of patients with HD and HF which may subsequently improve many of the MHCHF components and attenuate its viscous cycle. Recent position papers on cardiac rehabilitation suggest that low-load BFRE could be an adjunct exercise in cardiac rehabilitation for patients with HD who are frail with sarcopenia or other musculoskeletal disorders that may prevent moderate to high-intensity resistance training. (Ambrosetti et al., 2020; Hansen et al., 2022). In fact, a recent paper entitled "Is blood flow restriction resistance training the missing piece in cardiac rehabilitation of frail patients?" suggested that BFRE be started in the early phases of cardiac rehabilitation followed by moderate to high-intensity resistance training. (Kambic et al., 2022).

The purpose of this paper is to provide a comprehensive overview of the MHCHF and how BFRE may affect each component of the original and revised MHCHF and attenuate its viscous cycle. A systematic review of a growing literature of seven BFRE studies in HD and two BFRE studies in HF will follow in which the safety and beneficial effects of BFRE on the pathophysiological manifestations of HD and HF will be highlighted. (Nakajima et al., 2010; Fukuda et al., 2013; Madarame et al., 2013; Tanaka and Takarada, 2018; Groennebaek et al., 2019; Ishizaka et al., 2019; Kambič et al.,

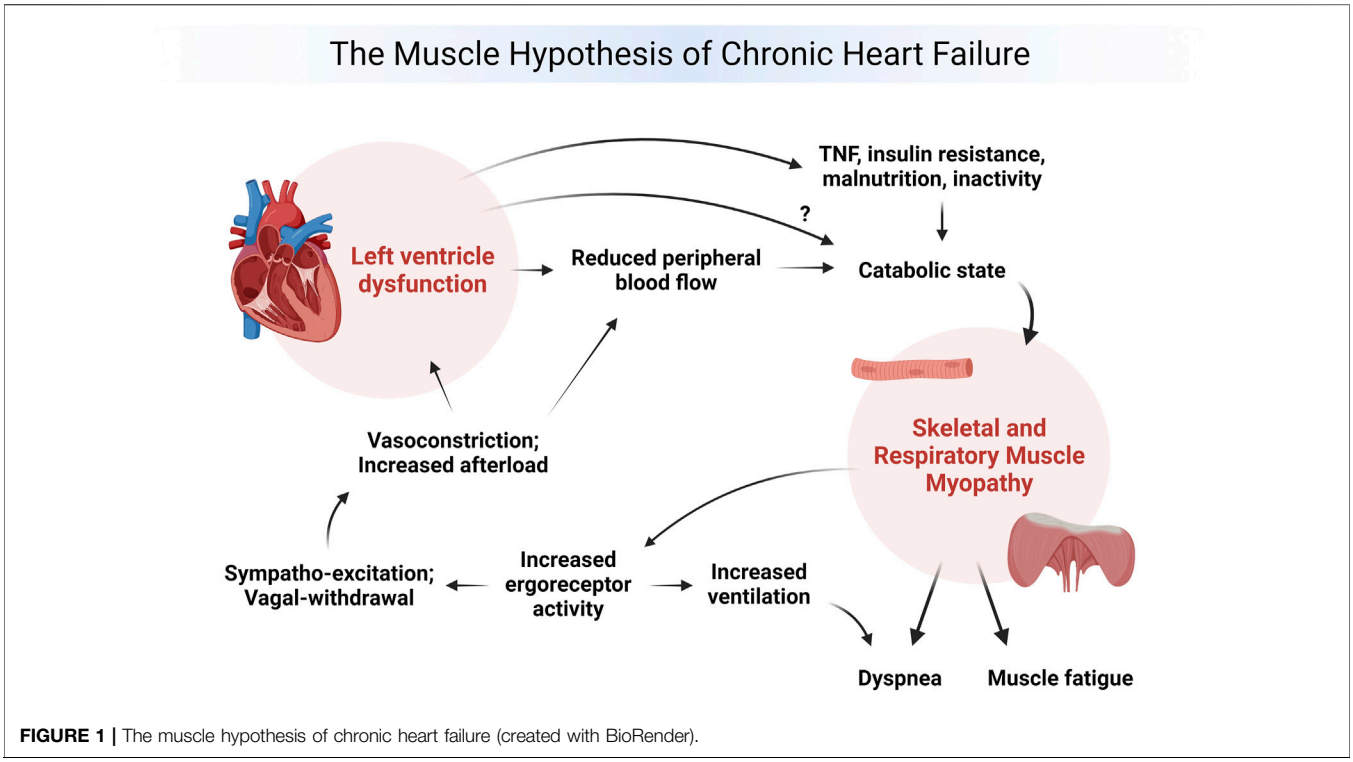

FIGURE 1 | The muscle hypothesis of chronic heart failure (created with BioRender).

2019; Kambič et al., 2021; Ogawa et al., 2021). Recent results from studies we have performed showing the beneficial effects of BFRE on cardiac and cardiovascular performance in patients with HF will also be presented. (Mostoufi et al., 2020; Gempel et al., 2022; Johnson et al., 2022). The paper will conclude with suggestions to safely perform BFRE in HD and HF using the currently available literature of BFRE in HD and HF.

THE MUSCLE HYPOTHESIS OF CHRONIC HEART FAILURE AND BLOOD FLOW RESTRICTION TRAINING

Patients with HF suffer from marked dyspnea and fatigue because of the inability of the heart to pump blood adequately to peripheral tissues resulting in excessive blood volume in the chambers of the heart and insufficient blood flow to skeletal muscles. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013). Insufficient blood flow to the skeletal muscles results in limited exercise tolerance, marked dyspnea and fatigue, further skeletal muscle weakness, and possibly a skeletal muscle metabolic myopathy. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013). Additionally, the excessive blood volume in the chambers of the heart results in a poorer capacity of the heart to pump blood to the periphery. (Christiansen et al., 2019; Li et al., 2022). In fact, the excessive blood volume in the cardiac chambers is a major target of pharmacologic treatment for HF and includes the administration of diuretics and vasodilators to decrease the excessive blood volume by reducing venous return and increasing peripheral vasodilation. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013).

The manner by which left ventricular dysfunction contributes to skeletal muscle weakness and many pathophysiological manifestations of heart failure have been keenly described in the MHCHF. This conceptual model outlines the major ramifications from HF on the body and identifies the major role that skeletal muscle weakness plays in worsening HF (**Figure 1**). As shown in **Figure 1**, left ventricular (LV) dysfunction due to HF initiates a viscous cycle of detrimental effects on the body including a reduction in peripheral blood flow, inactivity and elevated inflammatory markers, a catabolic and skeletal muscle myopathy including the respiratory muscles (contributing to the marked dyspnea and fatigue described above), and increased ventilation, SNS activity, and peripheral vasoconstriction all of which further worsen LV function and HF. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013). An improvement in skeletal muscle strength in HF may improve many of the pathophysiological manifestations of HF outlined above. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013).

In view of the potential effects of BFRE on the vasculature and cardiovascular function, it is possible that BFRE may be a potential method to improve not only skeletal muscle strength and endurance and exercise tolerance, but possibly even the pumping ability of the heart in HF. (Shweiki et al., 1992; Coats et al., 1994; Coats, 1996; Halliwill, 2001; Higashi and Yoshizumi, 2004; Takano et al., 2005; Chen and Bonham, 2010; Rossow et al., 2011; Horiuchi and Okita, 2012; Piepoli and Coats, 2013).

The three key mechanisms by which BFRE could potentially improve each area within the MHCHF include increasing skeletal muscle strength, decreasing venous return, and improving peripheral vasodilation (**Figure 1**). Since patients with HF suffer from marked dyspnea and fatigue, BFRE may provide an alternate form of exercise producing less dyspnea and fatigue while promoting greater muscle strength in a shorter period of time with a less frequent and intense exercise prescription. Additionally, the work of breathing during BFRE appears to increase which may facilitate a mild to moderate form of respiratory muscle training and attenuate the respiratory muscle metaboreflex. (May et al., 2017; Crisafulli et al., 2018). Decreasing venous return has the potential to improve cardiac filling pressures and LV dysfunction which alone could attenuate many of the pathophysiological manifestations of HF (**Figure 1**) while increasing skeletal muscle strength. The hypoxic state created during BFRE appears to up regulate hypoxia-inducible factor 1alpha (HIF-1A) which in turn promotes gene expression of vascular endothelial growth factor (VEGF) and promote angiogenesis. (Shimizu et al., 2016). Increased angiogenesis in the extremities may improve fluid flow dynamics and hypertension in patients with HF. In elderly individuals, 4-weeks of low intensity leg press with BFR significantly increased lower leg capillarity. (Patterson and Ferguson, 2011). Lastly, increasing endothelium-dependent vasodilation through BFR exercise is the same mechanism physicians use when treating HF by using a variety of pharmacologic agents. Therefore, BFRE appears to be a potential therapeutic modality to counter the viscous cycle of HF for which reason the below systematic review was performed.

Also, although the MHCHF was specifically designed for patients with HF, many of the components outlined in the original and revised MHCHF may still be present in patients with HD and other disorders such as chronic obstructive pulmonary disease and cachexia. (Coats et al., 1994; Coats, 1996; Piepoli and Coats, 2013). Examples of pathophysiologic manifestations in such patients include a reduction in cardiac output, inflammation, systemic catabolism, immobilization and deconditioning, autonomic nervous system abnormalities as well as skeletal muscle structural, metabolic, and functional abnormalities. Of course, the abnormalities in HF are much more profound, but as in HF, patients with HD may also have significant improvements in one or more of the above components of the MHCHF with BFRE.

METHODS

A comprehensive literature review was performed in PubMed and the Cochrane library through February 2022. **Supplementary Appendix S1** presents the complete search strategy which was conducted in English and included a mix of terms for the key concepts *blood flow restriction*, *heart disease*, *heart failure*, *physical function* and *skeletal muscle*. The reference list of eligible studies was also screened to identify other potentially relevant publications.

A study had to meet the following criteria to be included in the systematic review: 1) the study was original research conducted in human subjects older than 18 years of age and diagnosed with either heart disease or heart failure, 2) study participants performed BFRE, and 3) post-intervention outcome measures of cardiovascular function, physical performance, skeletal muscle function and structure, and/or systemic biomarkers were provided. Exclusion criteria included review articles and articles on viewpoints and opinions of BFRE, book chapters, theses, dissertations, and case study articles. Studies were only considered for eligibility if they have been peer reviewed and published prior to the search. Study quality was assessed using two separate instruments including the TESTEX scale for randomized controlled trials (RCTs) (Smart et al., 2015) and the National Institute of Health quality assessment tool for before-after (Pre-Post) studies with no control group. (NIH, 2021).

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

RESULTS

The search identified a total of 227 papers of which 9 met our inclusion criteria (7 reports of BFRE in HD and 2 reports of BFRE in HF) (**Figure 2**). The assessment of study quality revealed that 3 of the 5 RCTs were of a high quality with high reporting criterion while the other two RCTs were of modest quality and reporting criterion (**Table 1**). The assessment of study quality of the pre-post studies without a control group revealed that 3 of the studies were of a fair quality and one was of a good quality, but almost all studies were observed to have one or more areas of assessment that were either unable to determined, not reported, or not applicable (**Table 2**). A systematic review of each study will be provided below beginning with the studies that have examined the effects of BFRE in HF.

Blood Flow Resistance Training in Heart Failure

Both of the studies of BFRE in HF were RCTs and were performed without report of adverse events and observed significant improvements in several of the MHCHF components (**Table 3**). (Tanaka and Takarada, 2018; Groennebaek et al., 2019) The first study of BFRE in HF examined the effects of 6 months of bilateral aerobic BFRE with cycling performed at 40–70% of peak oxygen consumption for 15 min, 3x/week in 30 patients with both reduced and preserved ejection fraction heart failure who were randomized to either BFRE or control group. (Tanaka and Takarada, 2018). Pneumatic cuffs were placed proximally on both thighs and inflated to a pressure 40–80 mmHg above systolic blood pressure (mean ± SD of 208.7 ± 7.4 mmHg) and remained inflated during the entire cycling session. The control group performed the same intensity and duration of aerobic cycling, but without BFR. After the 6-months study period both the BFRE

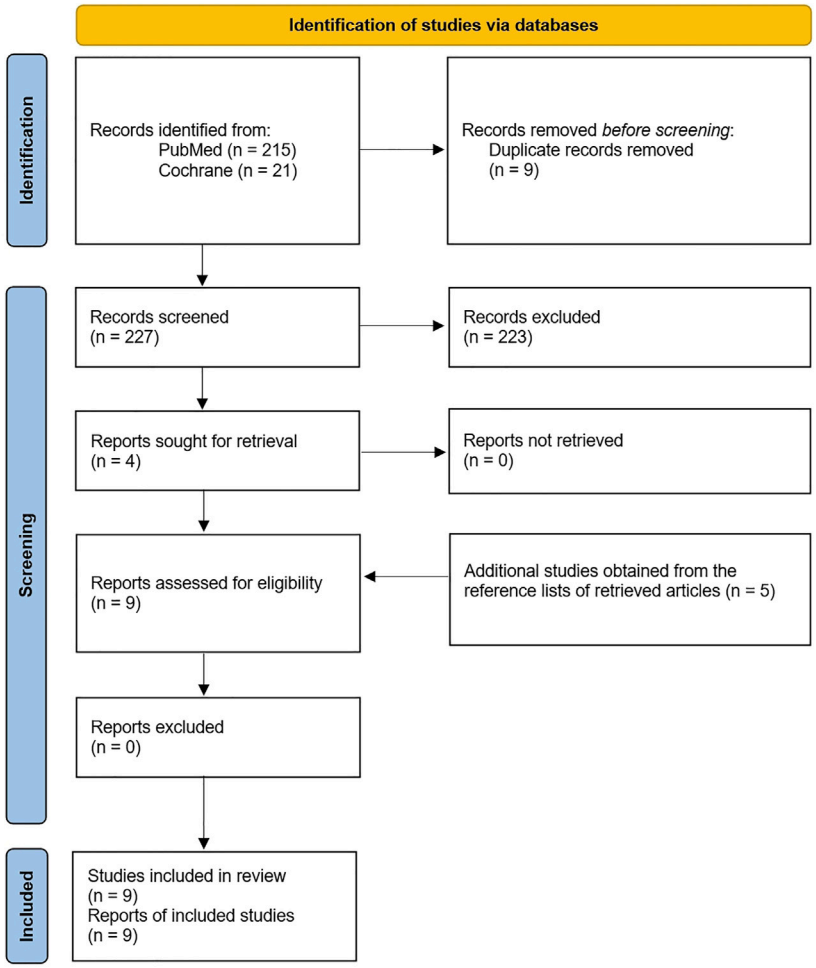

FIGURE 2 | Flow diagram of study selection.

TABLE 1 | TESTEX assessment of the quality and reporting of included randomized controlled trials.

	Study Quality Criterion						Study Reporting Criterion											
Study	1	2	3	4	5	Total	6a	6b	6c	7	8a	8b	9	10	11	12	Total	Overall Total
Tanaka and Takarada (2018)	1	1	0	1	0	3	0	1	0	0	1	1	1	0	0	1	5	8
Groennebaek et al. (2019)	1	1	0	1	1	4	1	1	1	1	1	1	1	0	1	1	9	13
Kambic et al. (2019) & Kambic (2020)	1	1	1	1	0	4	1	1	1	1	1	1	1	0	1	1	9	13
Ogawa et al. (2021)	1	0	0	1	0	2	0	1	0	0	1	1	1	0	1	1	6	8

TABLE 2 | National Institute of Health quality assessment of before-after (Pre-Post) studies with no control group of included studies.

	Itens													
Study	1	2	3	4	5	6	7	8	9	10	11	12	Total	QR
Nakajima et al. (2010)	1	0	1	CD	0	1	1	NR	NA	1	0	1	6	Fair
Madarame et al. (2013)	1	0	1	CD	0	1	1	NR	NA	1	0	1	6	Fair
Fukuda et al. (2013)	1	0	1	CD	0	1	1	NR	NA	1	1	1	7	Fair
Ishizaka et al. (2019)	1	1	1	1	0	1	1	NR	NA	1	1	1	9	Good

CD, cannot determine; NR, not reported; NA, not applicable; QR, quality rating.

TABLE 3 | Studies of blood flow restriction training in patients with heart failure.[a]

Author	Sample	Outcome measures	Procedures	Results
Tanaka and Takarada (2018)	30 male patients with both reduced and preserved EF heart failure due to MI with baseline EF, BNP, BUN, Creatinine, and eGFR in the BFR and non-BFR groups of 49.3 *vs*. 54.4, 148.1 *vs*. 144.5, 16.6 *vs*. 17.6, 1.0 *vs*. 1.0, 62.0 *vs*. 65.0, respectively. Patients were randomly assigned to the BFR group or control group performing aerobic exercise, but without BFR. Medications included ACE-I/ARB, Beta-blockers, Aldosterone antagonists, and statins with equal administration between groups except in ACE-I/ARB with a greater number of patients in the control group receiving ACE-I	Peak VO2, VO2 @AT, BNP, CRP, thigh circumference	Chronic (3x/week for 24 weeks) assessment of Aerobic BFR Ex. performed at 40–70% of peak VO2/W for 15 min/session. Aerobic BFR exercise was performed with pneumatic cuffs (90 mm wide and 700 mm in length) placed on the proximal ends of the thighs and inflated to a mean pressure of 208.7 mm Hg	No adverse events were reported. Peak VO2, VO2@AT, BNP, and CRP were significantly improved in the BFR Ex. group
Groennebaek et al. (2019)	36 male patients with heart failure reduced EF were randomly allocated to BFR, RIPC, or a control group receiving no intervention with respective EF of 35, 37, and 35%. Baseline BNP and eGFR in the BFR, RIPC, and control groups were 518, 297, and 188, respectively and 79, 84, and 89, respectively. Medications included ACE-I/ARB, Beta-blockers, sacubitril/valsartan, mineralocorticoids, diuretics, platelet inhibitors, and statins with equal administration between groups	Isometric strength, 6 MWT distance ambulated, QOL, skeletal muscle mitochondrial function	Chronic (3x/week for 6 weeks) assessment of Resistance BFR Ex. performed at 30% 1 RM with 50% of LOP while performing 4 sets of bilateral knee extension exercises with pneumatic cuffs inflated throughout the training period. RIPC was administer 3x/week for 6 weeks and consisted of 4 cycles of 5 min of upper arm ischemia followed by 5 min of reperfusion	No adverse events were reported. BFR Ex. significantly improved maximum isometric strength, 6 MWT distance ambulated, QOL, and mitochondrial function

[a]*The design of both studies of BFRE, in HF, were RCTs.*

and control group increased skeletal muscle strength and endurance reflected by increased Watts during cycle ergometry, but the BFRE group had a significantly greater increase in oxygen consumption compared to the control group (approximately 40 versus 10%, respectively). Other changes in the BFRE group that were not observed in the control group included a significant decrease in brain-natriuretic peptide (BNP) and C-reactive protein as well as a significant increase in oxygen consumption at the anaerobic threshold. Importantly, the improvement in BNP was significantly correlated in a negative direction to the improvement in peak oxygen consumption meaning that a greater reduction in BNP was associated with greater levels of peak oxygen consumption. (Tanaka and Takarada, 2018). The improvement in BNP and significant negative relationship with improvement in peak oxygen consumption is suggestive of improved cardiac performance due possibly to decreased preload from BFRE. (Takano et al., 2005; Tanaka and Takarada, 2018). Similar changes in BNP were also observed by Passino et al. after 9 months of aerobic exercise performed at 65% of the peak oxygen consumption heart rate 3x/week in patients with reduced ejection fraction heart failure, but without BFRE.[59] Also observed by Passino were significant favorable decreases in end-systolic and diastolic volume after the 9-months program as well as an identical significant relationship between BNP and peak oxygen consumption. (Passino et al., 2006). Although cardiac performance in the first study of BFRE was not examined, the above results of Passino et al. suggest that similar improvements in cardiac performance may have occurred in the Tanaka and Takarada study. (Passino et al., 2006).

The above studies highlighting a possible improvement in cardiac performance from exercise with and without BFRE prompted us to examine via echocardiography the acute effects of BFRE in two patients with HF one of whom had severe HF (LVEF = 25%) and the other with less severe HF (LVEF = 65%). (Johnson et al., 2022). A series of echocardiograms were obtained at rest and during 15 alternating straight leg raises (SLR) of each lower extremity performed supine without added resistance, with and without BFRE at a limb occlusion pressure of 60%. The key outcome measures included LVEF, stroke volume, and cardiac index with the hypothesis that improvements in the above measures would be observed in the patient with severe HF, but not in the patient with less severe HF. The results of the study found all outcome measures decreased in the patient with less severe HF, but improvements in all outcomes were observed in the patient with severe HF with an improvement in the cardiac index of almost 70%. (Johnson et al., 2022). The improvement in cardiac index of almost 70% was observed during SLR with BFRE and suggests an improvement in cardiac performance as well as peripheral blood flow.

In view of the above favorable changes in cardiac performance from BFRE in the patient with severe HF, chronic BFRE was

TABLE 4 | Studies of blood flow restriction training in patients with heart disease.

Author	Sample/Study design	Outcome measures	Procedures	Results
Nakajima et al. (2010)	7 stable male patients (mean ± SD age of 52 ± 4 yrs) with IHD (2 post-CABG surgery and 5 post-PTCA). Complete medication use was not reported, but all patients were administered Acetylsalicylic Acid or Ticlopidine Hydrochloride. The study design was a pre-post study without control group	Peak VO2, VO2 @AT, IGF-1, CRP, muscle CSA	Chronic assessment of BFR Ex using 4 sets (30 reps in the 1st set followed by 15 reps in subsequent sets with 60 s of rest between sets) of bilateral leg press, knee extension, and knee flexion at 20–30% of 1 RM 2x/week for 3 months with bilateral BFR (via KAATSU belt at proximal thighs using 100 mmHg cuff pressure initially which was gradually increased to 160–250 mmHg within 2–3 weeks to elicit a Borg RPE score of 16/20)	No adverse events were reported. BFR Ex produced a significantly greater CSA in the quadriceps, hamstring, and adductor muscles with significant increases in leg press, knee extension, and knee flexion 1 RM (approx. 15%) as well as significant increases in peak Watts, Watts @AT, peak VO2, and VO2 @AT. SBP and DBP were unchanged
Madarame et al. (2013)	9 stable patients (7 men, 2 women) with IHD (2 post-CABG surgery and 7 post-PTCA) with a mean ± SD age of 57 ± 6 yrs. Complete medication use was not reported, but patients were not administered anticoagulant drugs. The study design was a pre-post study without control group	HR, noradrenaline, D-dimer, fibrinogen/fibrin degradation products, CRP	Acute and chronic (1-h post Ex) assessment of BFR Ex using 4 sets (30 reps in the 1st set followed by 15 reps in subsequent sets with 30 s of rest between sets) of bilateral knee extension with and without BFR at 20% of 1 RM (via KAATSU belt at proximal thighs using 200 mmHg cuff pressure that was maintained throughout Ex and rest periods)	No adverse events were reported. BFR Ex produced a significantly greater HR and noradrenaline compared to non-BFR Ex. A significantly greater D-dimer and CRP was observed after BFR Ex compared to non-BFR Ex which were no longer statistically significant after plasma volume correction (suggesting that hemoconcentration was responsible for the significant increases in these measures). Plasma fibrinogen/fibrin degradation products were unchanged after both forms of Ex
Fukuda et al. (2013)	6 male patients (mean ± SD age of 69 ± 12 yrs) with IHD (5 post-MI and 1 dilated cardiomyopathy). Medication use was not reported. The study design was a pre-post study without control group	EMG and Borg RPE	Acute assessment of BFR Ex using Thera-Band (medium and light resistance bands) for 4 sets (30 reps in the 1st set followed by 15 reps in subsequent sets with 30 s of rest between sets) of bilateral elbow flexion with and without BFR at 20% of 1 RM (via KAATSU belt at proximal portion of both arms using 110–160 mmHg cuff pressure that was maintained throughout Ex and rest periods)	No adverse events were reported. BFR Ex produced significantly greater EMG and Borg RPE during all sets compared to non-BFR Ex
Kambic et al. (2019) &Kambic (2020)	24 mostly male patients (12/group) with IHD (13 NSTEMI, 11 STEMI) receiving PCI (N = 19) or CABG (*N* = 5) were randomly assigned to a BFR or control group with the control group performing aerobic exercise without BFR. Medication use included ASA and Statins in all patients with approximately 70% of the patients administered beta blockers and ACE/ARB agents. Both studies were RCTs	2019 report: 1-RM knee extension tests, vastus lateralis diameter, FMD, inflammatory markers, and fasting glucose and insulin sensitivity 2020 report: HR, BP, NT-proBNP, Fibrinogen, and D-dimer	2019 & 2020 report: Acute and chronic (2x/week for 8 weeks) assessment of BFR Ex. during knee extension and flexion using a pneumatic cuff (23 cm wide) compressing the medium portion of each thigh 15–20 mm Hg greater than resting brachial systolic blood pressure. Cuffs remained inflated throughout the 3 sets of 8, 10, and 12 reps at 30–40% 1-RM with 45-s rest periods between sets during which the cuffs remained inflated. Each leg was exercised separately as described above with a cadence of 1-s for the concentric phase and 2-s for the eccentric phase. Aerobic Ex. at 60–80% of HRmax for 35 min 3x/week was also performed in the BFR group and was also performed in the control group	2019 & 2020 report: No adverse events were reported 2019 report: BFR Ex. significantly increased muscle strength in the 1-RM and decreased systolic blood pressure with near significant improvements in FMD and insulin sensitivity 2020 report: Acutely, BFR Ex. produced significantly greater HR, SBP, and DBP during each of the 3 sets compared to baseline measures, but both the SBP and DBP were lower after the third set compared to the second set. Post-exercise HR, SBP, and DBP were significantly lower than the measures after each of the 3 sets. Chronically, SBP was significantly

(Continued on following page)

TABLE 4 | (*Continued*) Studies of blood flow restriction training in patients with heart disease.

Author	Sample/Study design	Outcome measures	Procedures	Results
				lower post-BFR compared to the control group performing aerobic Ex. No significant changes were observed in NT-proBNP, Fibrinogen, and D-dimer values
Ishizaka et al. (2019)	6 males with surgically repaired valvular heart disease and 1 female with MR, AR, and heart failure with baseline EF range of 20–66% who participated in the study 105–1,018 days from diagnosis of valvular heart disease. Medications included ACE-I/ARB, Beta-blockers, and calcium channel blockers. The study design was a pre-post study without control group	Maximal voluntary isometric knee extension bilaterally, EMG amplitude of the rectus femoris, vastus lateralis, and vastus medialis muscles during both concentric and eccentric contractions performed bilaterally which were also summed and averaged. Subjective Borg RPE with and without BFR was also measured	Acute examination of EMG activity at 10 and 20% of 1-RM with and without BFR. BFR was administered using the KAATSU system with 60 mm wide cuffs placed proximally around both thighs while participants were seated on the knee extension machine. The cuff pressure was set at 180 mmHg and the cuffs remained inflated throughout rest periods and were deflated between each of the 4 test conditions. The 4 test conditions that were examined included 10 and 20% of 1-RM with and without BFR with patients performing 3 sets of 30 bilateral knee extensions with 30 s of rest between sets and 5 min of rest between conditions. After completing the first test condition of 10% 1-RM without BFR the remaining 3 test conditions were administered using a block-randomization procedure	No adverse events were reported. All males completed the protocol, but the woman was only able to complete the 10% 1-RM protocol. BFR at 10% 1-RM significantly increased EMG amplitude of all muscles in both concentric and eccentric phases which was not significantly greater at 20% of 1-RM. The RPE increased significantly with BFR at both intensities and the RPE at 20% 1-RM with and without BFR was significantly greater than at 10% of 1-RM. Age was significantly correlated to EMG amplitude at several concentric and eccentric phases without BFR, but no significant correlations were found with BFR.
Ogawa et al. (2021)	21 mostly male patients early after cardiac surgery for mostly valvular heart disease with NYHA class 2–3 were randomly assigned to a BFR group or control group. Both groups attended outpatient cardiac rehabilitation 2x/week for 12 weeks with the addition of BFR Ex. to the BFR group. The mean EF and BNP of the BFR and control group was 54 and 59% and 303 and 172, respectively. Four patients in each group had atrial fibrillation and approximately 70% of the patients in each group were hypertensive. Medications administered to patients were not listed, but it appears that patients received thrombolytic agents during the early phase of rehabilitation. The study design was a RCT.	Body weight and composition, blood biochemistry, maximal voluntary isometric contraction of the knee extensors and handgrip, muscle size, and adverse effects	Early and chronic examination of BFR and cardiac rehabilitation versus cardiac rehabilitation alone. BFR was administered 2x/week using the KAATSU system with cuffs placed proximally around both thighs and cuff pressure increased from 100 mmHg to 160–200 mmHg over a 2–3-week period. BFR Ex. started 5–7 days after surgery if patients were able to walk 200 m and consisted of bilateral knee extension and flexion and leg press. BFR Ex. was started at a low-intensity (a single set of 20 repetitions with 5–10 kg and 20–30 kg for knee extension and flexion and leg press, respectively) and was progressed to 3 sets of 30 repetitions for each exercise with a 30 s rest between sets at 20–30% of 1-RM. The Borg RPE was used to monitor and control exercise and was consistently kept below 15	No adverse events were reported and CPK and D-dimer were normal after the 12 weeks study period. Early after cardiac surgery the BFR group had significantly greater body weight, anterior mid-thigh muscle thickness, and skeletal muscle mass while the control group had no significant improvement. Compared to early after surgery upon completion of the 12-weeks study, the BFR group was found to have a significant increase in body weight, anterior mid-thigh muscle thickness, skeletal muscle mass, walking speed, and knee extensor strength while no significant change from early after cardiac surgery to completion of the study was found in the control group. Low functioning patients tended to increase functional performance more than high functioning patients

performed via SLR without added resistance 2x/week for 3 weeks at 60% limb occlusion pressure. (Gempel et al., 2022). Three sets of 15 alternating SLR of each leg were performed in supine and followed by deflation of the cuffs after each set for a period of 5 min. The patient suffered from gastrointestinal distress before BFRE while participating in cardiac rehabilitation which appeared to be worsened by BFRE for which reason BFRE was terminated after 3 weeks. Despite this, the patient was observed to have a 50% improvement in SLR ability as well as a 13 and 12.5% increase in knee extensor and hip flexor strength, respectively, without change in cardiac performance. (Gempel et al., 2022). Additionally, the average increase in heart rate, systolic and diastolic blood pressure

was 15 bpm, 10 mmHg, and 2 mmHg, respectively, with average Borg RPE, modified dyspnea, and lower extremity pain scores of 12/20, 1/10, and 7/10, respectively. No adverse events were observed during the above two echocardiographic studies. (Gempel et al., 2022; Johnson et al., 2022).

The second study of BFRE in HF was performed by Groennebaek et al. in which 36 patients with reduced ejection fraction heart failure (LVEF = 35–37%) were randomized to BFRE, remote ischemic preconditioning (RIPC), or non-treatment control (**Table 3**). (Groennebaek et al., 2019) BFRE and RIPC were performed 3x/week for 6 weeks. BFRE consisted of resistance exercise performed at 30% of 1 RM with 50% limb occlusion pressure during which 4 sets of bilateral knee extension exercise separated by 30-s rest periods with a pneumatic cuff inflated until the 4 sets were completed. The RIPC protocol consisted of 4 cycles of 5 min upper arm ischemia followed by 5 min of reperfusion. The results of the study found BFRE produced significant improvements in maximal isometric strength, mitochondrial function, 6-min walk test (6 MWT) distance ambulated, and quality of life which were not observed in the RIPC or control groups. Thus, in view of the above results, patients with HF performing aerobic exercise, functional exercise, and resistance training improve skeletal muscle strength and endurance, mitochondrial function, oxygen uptake, 6 MWT, and quality of life as well as the possibility of improved cardiac function. Furthermore, none of the above studies observed adverse events.

Blood Flow Resistance Training in Heart Disease

Three of the 7 studies of BFRE in HD were RCTs (Kambic et al., 2019; Kambic, 2020; Ogawa et al., 2021) and the other 4 studies were pre-post studies without control groups. All of the 7 studies examined the effects of resistance BFRE and all were performed without report of adverse events and also observed significant improvements in several of the MHCHF components (**Table 4**). Five of the 7 studies of BFRE in HD were performed in Japan with all of the 5 studies using KAATSU cuffs bilaterally and with all but one study placing the cuffs on the most proximal portion of the thigh. The other Japanese study placed the cuffs on the most proximal portion of the arms bilaterally and had patients perform 4 sets of bilateral elbow flexion (starting with 30 repetitions followed by 3 sets of 15 repetitions) with and without BFR at 20% of 1 R M and with 30 s of rest between sets. (Fukuda et al., 2013). The 4 other Japanese BFRE studies in patients with HD performed bilateral knee extension at 20% of I-RM starting with 30 repetitions followed by 3 sets of 15 repetitions with and without BFR with 30 s of rest between sets (Madarame et al., 2013) while Ishizaka used the same muscle groups and protocol except that they also examined EMG activity using 10% of 1-RM and provided 5 min of rest between each of the 4 study conditions. (Ishizaka et al., 2019). One of the Japanese studies performed bilateral knee extension and flexion as well as bilateral leg press at 20–30% of 1-RM, 2x/week for 3 months using 30 repetitions followed by 3 sets of 15 repetitions with BFR and with 60 s of rest between sets. (Nakajima et al., 2010). The last Japanese study examined the effects of cardiac rehabilitation with and without BFRE during which BFRE started 5–7 days after surgery if patients were able to walk 200 m and consisted of bilateral knee extension and flexion as well as leg press at 20–30% of 1-RM using 3 sets of 30 repetitions with a 30 s rest between sets. (Ogawa et al., 2021).

The results of the above studies are shown in **Table 4**. The Nakajima et al. study found a significantly greater cross-sectional area of the quadriceps, hamstring, and adductor muscles with significant increases in leg press and knee extension and flexion as well as increases in peak watts, watts at the anaerobic threshold, peak oxygen consumption, and oxygen consumption at the anaerobic threshold without change in blood pressure. (Nakajima et al., 2010). The study by Madarame observed a significantly greater heart rate and noradrenaline response compared to non-BFRE as well as a significantly greater D-dimer and CRP after BFRE compared to non-BFRE which were no longer statistically significant after plasma volume correction (suggesting that hemoconcentration was responsible for the significant increases in these measures). Plasma fibrinogen/fibrin degradation products were unchanged after both forms of exercise. (Madarame et al., 2013). The study by Fukuda et al. found that BFRE produced significantly greater EMG and Borg RPE during all sets compared to non-BFRE. (Fukuda et al., 2013). The study by Ishizaka et al. observed that BFRE at 10% 1-RM significantly increased EMG amplitude of all muscles in both concentric and eccentric phases which was not significantly greater at 20% of 1-RM. (Ishizaka et al., 2019). The RPE increased significantly with BFR at both intensities and the RPE at 20% 1-RM with and without BFRE was significantly greater than at 10% of 1-RM. Also, age was significantly correlated to EMG amplitude at several concentric and eccentric phases without BFRE, but no significant correlations were found with BFRE. The study by Ogawa et al. found CPK and D-dimer were normal after the 12-weeks study period. Early after cardiac surgery, the BFR group had significantly greater body weight, anterior mid-thigh muscle thickness, and skeletal muscle mass while the control group had no significant improvement. Compared to early after surgery upon completion of the 12-weeks study, the BFR group was found to have a significant increase in body weight, anterior mid-thigh muscle thickness, skeletal muscle mass, walking speed, and knee extensor strength while no significant change from early after cardiac surgery to completion of the study was found in the control group. Low functioning patients tended to increase functional performance more than high functioning patients. (Ogawa et al., 2021) (**Table 4**).

The two other studies of BFRE in HD were performed in Slovenia using the same patient population while using a pneumatic cuff that was placed at the medium portion of each thigh (**Table 4**). The acute and chronic effects of BFRE were examined in patients with ischemic HD who were randomized to BFR or control group. The BFRE group performed knee extension and flexion 2x/week for 8 weeks with 3 sets of 8, 10, and 12 repetitions at 30–40% of 1-RM with 45-s rest periods between sets during which the cuffs remained inflated. Each leg was exercised separately with a cadence of 1-s for the concentric phase and 2-s for the eccentric phase. The cuff pressure was inflated 15–20 mmHg above resting brachial systolic pressure. The control group and the BFRE group performed aerobic exercise at 60–80% of maximal heart rate for 35 min, 3x/week

during the 8-weeks study period. In the chronic study, BFRE significantly increased muscle strength in the 1-RM and decreased systolic blood pressure with near significant improvements in flow mediated dilation and insulin sensitivity. In the acute study, BFRE produced significantly greater HR, SBP, and DBP during each of the 3 sets compared to baseline measures, but both the SBP and DBP were lower after the third set compared to the second set. Also, post-exercise HR, SBP, and DBP were significantly lower than the measures after each of the 3 sets and no significant changes were observed in NT-proBNP, Fibrinogen, and D-dimer values. Furthermore, in the chronic study, SBP was significantly lower post-BFR compared to the control group performing aerobic exercise alone (**Table 4**).

DISCUSSION

It is important to note that BFRE was performed safely in all of the above studies without report of an adverse event.[41-49] This is an important finding given that a variety of patients with HD (CABG and valvular surgery, PTCA, non-ST segment elevation MI and ST-segment elevation MI, dilated cardiomyopathy, and heart failure) performed BFRE making the results of this systematic review more generalizable. However, the relatively small number of total subjects in this systematic review (n = 140; 74 with HD and 66 with HF) and the carefully selected subjects with the HF subjects having mild to moderate HF based on BNP values highlights the need for further investigation of BFRE in HD and HF.

The results of the chronic BFRE by Nakajima et al. appear to be most promising for patients with HD in view of the significantly greater circumferential surface area in the quadriceps, hamstring, and adductor muscles, significant increases in leg strength, as well as submaximal and maximal exercise and cardiorespiratory capacity after 3 months of twice weekly BFR exercise performed at 20–30% 1 RM with an initial set of 30 repetitions followed by 3 sets of 15 repetitions and a 60 s rest between sets. (Nakajima et al., 2010). Thus, a short exercise duration (30–60 s x 4 = 120–240 s) performed with a low frequency (2x/week) and workload (20–30% 1 RM) yielded important results commonly found after much longer and more frequent exercise performed at a higher intensity. (Nakajima et al., 2010). Similar results were observed in the other four studies of chronic BFRE in HD. (Madarame et al., 2013; Kambič et al., 2019; Kambič et al., 2021; Ogawa et al., 2021). These are important factors for patients with HD who may be unable to exercise at the intensity, duration, and frequency needed to elicit similar changes using aerobic or more traditional resistance training. In fact, the improvement from BFRE in strength, exercise, and cardiorespiratory capacity was very similar to that observed after aerobic exercise performed at a greater intensity, duration, and frequency. (Passino et al., 2006).

The results of the acute and chronic BFRE studies in HD are also important since plasma fibrinogen and fibrin degradation products were unchanged and after plasma volume correction, the D-dimer and CRP values were no longer statistically different than before BFR exercise highlighting the potential safety of BFRE in patients with HD. (Madarame et al., 2013; Kambič, 2020). Furthermore, 38% of the patient population in the Ogawa et al. study had atrial fibrillation which has been a potential concern when considering BFRE in patients with HD and HF. It is also important to note that all of the BFRE studies presented in **Table 3**, **Table 4** were performed upright and not in a supine position with all but one study performing BFRE in the lower extremities bilaterally with the one study not performing BFRE to the lower extremities performing BFRE in the upper extremities bilaterally. The use of bilateral upper extremity BFRE in patients with HD is likely to elicit a greater cardiovascular response than found in lower extremity BFRE and requires further investigation in patients with HD. One possible alternative may be unilateral versus bilateral BFRE in patients with HD or HF in need of improving upper extremity strength and endurance.

Although no studies of BFRE in HD utilized aerobic exercise training, the results of BFRE in HF are promising especially since aerobic BFRE appears to elicit a less aggressive hemodynamic response. (May et al., 2017; Tanaka and Takarada, 2018). Furthermore, the results of bilateral lower extremity BFRE with a cyclical occlusion and reperfusion protocol may elicit similar findings to those we observed in patients with HF. (Gempel et al., 2022; Johnson et al., 2022). Such effects could improve cardiac rehabilitation efforts by prescribing lower intensity exercise and eliciting a favorable cardiovascular response while increasing skeletal muscle strength and hypertrophy and possibly improve cardiac performance. However, further investigation of the effects of cyclical occlusion and reperfusion on skeletal muscle strength and hypertrophy as well as cardiovascular function in patients with HD and HF is needed. Despite this, the methods employed in the studies included in this systematic review that resulted in safe BFRE with significant improvements in many MHCHF components have been listed in **Table 5** along with other factors that are considered important in the rehabilitation of patients with HD and HF. (Ambrosetti et al., 2020; Hansen et al., 2022). Although the suggested methods require further investigation and testing, they provide a framework to apply BFRE in the rehabilitation of patients with HD and HF. Limitations to this systematic review include the relatively small number of total subjects and the carefully selected subjects with the HF subjects having mild to moderate HF based on BNP values highlighting the need for further investigation of BFRE in HD and HF. Furthermore, investigation of feasibility, acceptability, adherence, adverse effects, and symptoms during and after BFRE is needed since very few studies have examined these important issues comprehensively in patients with HD and HF.

In summary, BFRE in HD and HF was performed safely and was observed to improve one or more of the following measures in the reviewed studies including skeletal muscle strength, endurance, and hypertrophy; cardiorespiratory performance; mitochondrial function; exercise tolerance; functional performance; immune humoral function; and possibly cardiac performance. (Nakajima et al., 2010; Fukuda et al., 2013; Madarame et al., 2013; Tanaka and Takarada, 2018; Groennebaek et al., 2019; Ishizaka et al., 2019; Kambič et al.,

TABLE 5 | Suggested methods to perform blood flow restriction training safely in patients with heart disease and heart failure.

1. Review risk factors for potential reasons to not perform BFRE including unstable or uncontrolled heart disease or heart failure, rapid and uncontrolled cardiac dysrhythmias, severe pulmonary hypertension or severe cardiac disease (valvular heart disease, myocarditis, endocarditis, pericarditis), history of venous thromboembolism, severe varicose veins, uncontrolled hypertension (> 180/110 mmHg), and an acute systemic illness
2. Discuss with the patient functional limitations and activities of daily living that are difficult to perform to target muscle groups in need of strengthening and aerobic conditioning
3. Obtain the resting heart rate, electrocardiogram (ECG), blood pressure, respiratory rate, rating of perceived exertion (RPE), symptoms, appearance and possibly girth measurements of the targeted extremities in sitting and/or supine. Examine the targeted extremities for signs, symptoms, and history of venous stasis and venous thrombosis
4. Educate patients about the procedures involved with blood flow restriction exercise
5. Determine the 1 repetition maximum (1-RM) using one of several different methods for the targeted muscle groups and repeat 1-RM measurements weekly or every 2–4 weeks to progress BFR resistance exercise. Determine peak oxygen consumption to prescribe aerobic BFRE at a specific percentage of the peak level and possibly use a percentage of age-predicted maximal heart rate and heart rate reserve if measurement of peak oxygen consumption is not possible
6. Apply the blood flow restriction cuff to one or both of the targeted proximal extremities and inflate it to the desired limb occlusion pressure
7. Obtain the post-cuff inflation heart rate, blood pressure, respiratory rate, rating of perceived exertion, symptoms, ECG, and appearance of the targeted extremity or extremities and compare to the values obtained in sitting and/or supine
8. Perform exercise with the inflated blood flow restriction cuff to the targeted extremity while continuously monitoring symptoms and the ECG, and measuring the heart rate, blood pressure, respiratory rate, rating of perceived exertion, and appearance of the exercising extremity after each set of exercise and compare to resting values and each set of exercise. a. Blood flow restriction resistance training: 3–4 sets of 15–30 repetitions at 20–30% of 1-RM with 30–60 s rest periods between sets, 2–3x/week b. Blood flow restriction aerobic training: Aerobic exercise such as treadmill ambulation or cycle ergometry performed at 40–70% of peak oxygen consumption for 10–15 min, 2–3x/week
9. Deflate and remove the blood flow restriction cuff and obtain the symptoms, heart rate, blood pressure, respiratory rate, rating of perceived exertion, ECG, appearance and possibly girth measurements of the targeted extremity and compare to the values obtained in sitting and/or supine
10. Terminate BFRE if any of the following occur including: a) symptoms associated with heart disease (angina, dyspnea, dizziness, etc.) or heart failure (dyspnea and fatigue), b) a hypertensive or hypotensive blood pressure response, c) ECG abnormalities, d) an abnormal heart rate, respiratory rate, or RPE response, d) marked peripheral edema in targeted extremity, e) signs or symptoms of venous stasis or venous thrombosis

2019; Kambič et al., 2021; Ogawa et al., 2021). Although these results are promising, further investigation of BFRE in patients with HD and HF is needed in view of the beneficial effects on skeletal muscle, functional performance, and cardiorespiratory function in older subjects without heart disease. (Hughes et al., 2017; Beckwée et al., 2019; Centner et al., 2019; Van Cant et al., 2020; Nitzsche et al., 2021; Rodrigo-Mallorca et al., 2021; Labata-Lezaun et al., 2022). Finally, there is a distinct need for additional randomized controlled trials examining the effects of BFRE in patients with HD and HF.

CONCLUSION

In view of the above systematic review, BFRE has been performed safely with no report of adverse event in patients with a variety of different types of HD and in patients with HF. The available literature suggests that many components of the MHCHF are improved with BFRE which may attenuate its viscous cycle. The components of the MHCHF that can be potentially improved with BFRE include left ventricular dysfunction, inflammatory markers, inactivity, a catabolic state, skeletal and possibly respiratory muscle myopathy, dyspnea and fatigue, ANS activity, and peripheral blood flow. Although the currently available BFRE literature has demonstrated improvements in each of these components in patients with HD and HF, further investigation of the role BFRE may have in the management of HD and HF is needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LC and MF contributed to conception and design of the study. LC, MF, JO, BA, and LH contributed substantially to data analysis and interpretation, and the writing of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

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Differences in the limb blood flow between two types of blood flow restriction cuffs: A pilot study

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Introduction: The determination of the optimal occlusion level is a key parameter in blood flow restriction (BFR). This study aimed to compare the effects of elastic (BStrong) vs. nylon (Hokanson) BFR cuffs on blood flow in the lower and upper limbs.

Methods: Eleven healthy participants undertook several BFR sessions with 2 different cuffs of similar width on their lower and upper limbs at different pressures [200, 250, 300, 350, and 400 mmHg for BStrong and 0, 40, and 60% of the arterial occlusion pressure (AOP) for Hokanson]. Doppler ultrasound recorded blood flows through the brachial and femoral artery at rest.

Results: With BStrong, only 350 and 400 mmHg pressures were significantly different from resting values (0% AOP). With Hokanson, both 40% and 60% of the AOP were significantly different from resting values ($p < 0.05$).

Discussion: While both cuffs elicited BFR, they failed to accurately modulate blood flow. Hokanson is appropriate for research settings while BStrong appears to be a convenient tool for practitioners due to its safety (i.e., the impossibility of completely occluding arteries) and the possibility of exercising freely detached from the pump.

KEYWORDS

vascular occlusion, BFR, BStrong, Hokanson, ultrasound

Introduction

Blood flow restriction (BFR) is a training method that attracted scientific interest very early (Shinohara et al., 1997). It has been since increasing in popularity. This method consists of restricting blood flow via occlusion cuffs placed proximally on limbs during training exercises, for example, weightlifting. BFR partially restricts arterial inflow and generally, fully restricts venous outflow. Numerous studies to date have shown beneficial

Abbreviations: AOP, Arterial occlusion pressure; BFR, Blood flow restriction; bSBP, Brachial systolic blood pressure.

muscle adaptations of the BFR method. There is a general consensus that low-load BFR training induces gains superior to low-load training, but does not surpass that of traditional high-load resistance training (Hughes et al., 2017; Patterson et al., 2019). The mechanisms responsible for increased strength and muscle gains appear to be multicausal. It has been suggested to be related to metabolite accumulation, fast-twitch fiber recruitment, and mTOR signaling (Wernbom et al., 2008; Loenneke et al., 2010; Scott et al., 2014).

The use of BFR has been shown to be beneficial for populations such as athletes, the elderly, or patients undergoing rehabilitation. Importantly, it has been thus far approved as a safe method for healthy subjects (Loenneke et al., 2011). It has also been applied to at-risk populations (e.g., with obesity, diabetes, cerebrovascular diseases, neuromuscular diseases, orthopedic diseases, respiratory diseases, hypertension, or cardiac diseases) (Nakajima et al., 2006).

Applied pressure plays an important role in BFR. When pressure is too low, no blood flow, metabolic, or muscle changes are observed while a too high pressure may increase discomfort without further blood flow decrease (Mattocks et al., 2017). It has been recommended to set applied pressure based on the measurement of arterial occlusion pressure (AOP) since it takes into account the characteristics of the cuff and the individual, which account for large influences in the occlusion stimulus (Patterson et al., 2019). For example, larger limb sizes require greater pressure (Loenneke et al., 2012; Barnett et al., 2016) and wider cuffs require lower pressure (Mattocks et al., 2018; Patterson et al., 2019). However, it is still unclear if cuffs of the same size, but different materials present significant differences. This latter point is of primary importance considering the wide variety of cuffs available on the market. In the literature, elastic or nylon cuffs have been mostly used. Nylon and elastic cuffs of the same size (5 cm) have been compared but no significant difference was found in the AOP measured at rest in the supine position in the lower body (Loenneke et al., 2013). In another study, the authors chose to measure repetitions to exhaustion as a surrogate marker of blood flow changes. They found no difference in repetition to exhaustion and perceptual responses between narrow elastic and narrow nylon cuffs of the same width (Loenneke et al., 2014). Conversely, it was shown that elastic cuffs had higher AOP than nylon cuffs of similar width at rest in the upper body (Buckner et al., 2017). That said, when applied at the same %AOP, there were no differences in the repetitions to volitional failure suggesting that the reduction in blood flow was similar between cuffs. Thus, differences in cuff material could be corrected simply by using the % AOP (Patterson et al., 2019). In addition, novel BFR equipment cannot occlude completely blood flow (e.g., BStrong) and for this reason prevents the risks associated with the potential unsafe use of the cuffs (e.g., excessive duration and level of the pressure applied). However, the %AOP cannot be used with this characteristic.

Therefore, given the controversial results regarding the material effect on AOP, this study aimed to compare a new and less costly elastic cuff system (BStrong) to a rigid nylon cuff system commonly used in the literature (Hokanson) on blood flow in lower and upper limbs measured at rest in a sitting position. From a practical point of view, it also intended to provide recommendations on the pressures to be applied when using BStrong cuffs. We hypothesized that elastic cuffs would require higher pressure than nylon cuffs to obtain the same BFR.

Methods

Experimental approach to the problem

This study evaluated the blood flow with Doppler ultrasound after applying different pressure levels in random order with two cuffs systems (BStrong vs. Hokanson) in the lower and upper limbs.

Participants

Eleven healthy subjects (7 women and 4 men) agreed to participate in this study. Participants' age, height, body mass, systolic and diastolic blood pressures were 26.3 ± 3.7 years, 173 ± 8 cm, 69.6 ± 13.7 kg, 123.4 ± 19.3 mmHg, and 75.5 ± 12.7 mmHg, respectively. The participants did not have any injury and no skeletal or muscle pain in the past 3 months. In addition, participants were required to have no blood clotting problems, nor be consuming aspirin or anticoagulants. Furthermore, no participants had performed any intense training before the start of the experiment. The local Ethical Committee approved the entire experimental protocol (2018–02298), and participants gave their written informed consent.

Material

The Hokanson model 10 cm cuff (SC10, 11 × 85 cm cuff size, 10 × 41 cm bladder size; Hokanson, Bellevue, WA, United States) was used for the lower body and the 5 cm cuff (SC5, 6 × 83 cm cuff size, 5 × 41 cm bladder size; Hokanson, Bellevue, WA, United States) was used for the upper body. To allow for the best possible comparison, BStrong cuffs that most closely resembled the Hokanson system in width were chosen: the yellow cuff (BStrong, Park City, UT; 54–79 cm long; 7.5 cm wide), which is the widest, was chosen for the lower body, and the green cuff (18–31 cm long; 5 cm wide) for the upper body. The red cuff (26–45 cm long; 5 cm wide) was used only on one participant's upper body, which had a larger arm circumference.

Procedures

After verifying eligibility, the blood pressure was measured with an automatic blood pressure monitor (Omron RX-I, model HEM-632-E) at rest in a sitting position to identify any potential hypertension. Measurements were taken at the right wrist with the arm at the level of the heart. Two blood pressure measurements were taken and averaged. In addition, the circumference of the limbs was measured on all recorded limbs

using metric tape. The measurements with either BStrong or Hokanson started in a randomized order. The first limb and the first side to be occluded were also randomly assigned. A break of 2 min was observed between each measurement. Throughout the measurements, the participants remained seated at rest on a chair with feet flat on the floor.

As reported above, the maximal available pressure with BStrong does not lead to arterial occlusion while lower pressures completely occlude blood flow with Hokanson. Therefore, using the same pressures with the two cuffs models would not have been appropriate and thus, different levels of pressure between both systems were used.

The experiment with BStrong started by placing the deflated elastic cuff on the proximal part of the limb to be occluded. The pressure in the cuff was increased using a hand-held pressure gauge up to 200, 250, 300, 350, and 400 mmHg randomly to account for possible effects of time order. Each time, once the pressure was maintained for 1 min, blood flow was recorded for 30 s by a linear Doppler (L12-5L60N) coated with ultrasound gel placed on either the brachial or femoral artery. Doppler ultrasound was used to obtain a real-time image of the measured artery using EchoWave II 3.4.4 software (version 3.4.4, Telemed Medical Systems, Telemed Ltd. Lithuania, Milano, Italy).

The experiment with Hokanson was conducted similarly except that it started with the determination of the AOP and that the pressure was increased up to 0%, 40%, and 60% of the AOP in random order. To determine AOP, the blood flow was detected with the Doppler probe, and the pressure in the cuff was gradually increased using an E20 Rapid Cuff Inflator (Hokanson, Bellevue, WA, United States) until no blood flow was detected in the artery, which was defined as the AOP. The cuff was deflated immediately afterwards. This measurement was repeated 2 to 3 times and averaged to record an accurate and reliable AOP value.

Data analysis

The data were processed using EchoWave II software. The diameters of the brachial and femoral arteries were measured manually using digital calipers. The values were averaged over 10 measurements throughout 30 s of recording for each of the 8 pressures applied with the two cuff systems (0%, 40%, and 60% with Hokanson cuffs and 200, 250, 300, 350, and 400 mmHg with BStrong cuffs). Based on the diameter of the vessel (in mm), the EchoWave software allowed calculation of the blood flow values ($ml{\cdot}min^{-1}$). The mean ± SD were thereafter calculated for each limb. Outliers, i.e., values of more than ±2 SD from the mean were removed.

Statistical analysis

Data are presented as mean ± SD. A repeated-measures three-way ANOVA was used to compare resting blood flow values ($ml{\cdot}min^{-1}$) between different pressures between the two types of cuffs (BStrong vs. Hokanson) but also to compare whether there was a significant difference between the arms or legs and between the left or right side. The normality of the data distribution was assessed using the Shapiro-Wilk test. Mauchly's test was used to test the assumption of sphericity. Where this assumption was violated ($p < 0.05$), the Greenhouse-Geisser (if Epsilon <0.75) or Huynh-Feldt (if Epsilon >0.75) corrections were used. In the case of a significant interaction, multiple comparisons (post hoc tests) corrected using the Tukey method were performed. Effect sizes were calculated using Cohen's methods. The threshold for statistical significance was set to $p < 0.05$. All data were analyzed using Jamovi statistical software version 1.1.9 (Jamovi Project, Sydney, Australia).

Results

Table 1 presents the measurements of the arms and legs circumference of each participant and the pressures that were needed to obtain a complete arterial occlusion with the Hokanson system. The average AOP was 208.5 ± 29.2 mmHg with Hokanson, whereas such pressure applied using BStrong did not lead to blood flow significantly different from resting values (0% of the AOP). Even the highest BStrong pressure (400 mmHg) did not completely occlude blood flow.

Figure 1 represents the blood flow values with BStrong and Hokanson systems in all four limbs. The two BFR systems were able to significantly reduce blood flows compared to resting values. A pooled analysis between limbs revealed that, with BStrong, only 350 ($p = 0.016$, $d = 0.688$) and 400 mmHg ($p = 0.002$, $d = 0.805$) pressures were significantly different from resting values (0% AOP). With Hokanson, both 40% ($p = 0.009$, $d = 0.715$) and 60% ($p < 0.001$, $d = 0.948$) of the AOP were significantly different from resting values ($p < 0.05$). However, while the two highest BStrong pressures decreased the blood flow compared to resting values (0% of the AOP), BStrong was not able to regulate blood flow according to the pressure applied (no significant differences were found between each of the pressure applied). This was also the case with Hokanson, however to a lesser extent. The blood flows tended to slightly decrease as the pressure in the cuff was increased. Significant differences were found between 0 and 40% of the AOP ($p = 0.009$) but not between 40 and 60% of the AOP. In addition, there were significant differences in blood flow between limbs ($p = 0.017$, $d = 0.487$) and sides ($p = 0.028$, $d = 0.287$).

Discussion

This study aimed to compare two cuff systems (BStrong vs. Hokanson) of different materials (elastic vs. nylon, respectively) with similar widths. This is the first work to compare BStrong to Hokanson, a device commonly used in research. It also strived to

TABLE 1 Arterial occlusion pressures (AOP) measured at rest with Hokanson and circumference of participants' limbs.

Participants	Right arm		Left arm		Right leg		Left leg	
	Circumference (cm)	AOP (mmHg)	Circumference (cm)	AOP (mmHg)	Circumference (cm)	AOP (mmHg)	Circumference (cm)	AOP (mmHg)
1	26	200	25.5	189	54	254	54	200
2	29.4	202	29.1	210	59.6	259	59.2	183
3	32.7	197	32.5	210	60.4	204	60.8	214
4*	29.1	190	29.6	192	58.1	178	58.2	156
5	30.6	227	30.2	186	56.8	206	56.7	198
6*	34.6	222	35.7	257	58.3	223	59.4	231
7	32.2	237	31.4	256	58.2	208	56.7	190
8	36.7	244	N/A	N/A	67.1	262	N/A	N/A
9	34.2	217	N/A	N/A	60.9	217	N/A	N/A
10	N/A	N/A	29.2	216	N/A	N/A	54.6	181
11	N/A	N/A	27.8	160	N/A	N/A	53.8	142
Mean	31.7	215.1	30.7	208.4	59.3	223.4	58.1	188.3
SD	3.3	18.9	3.4	32	3.6	29	4.1	27.4

*Left-handed participants. N/A because only one side was measured.

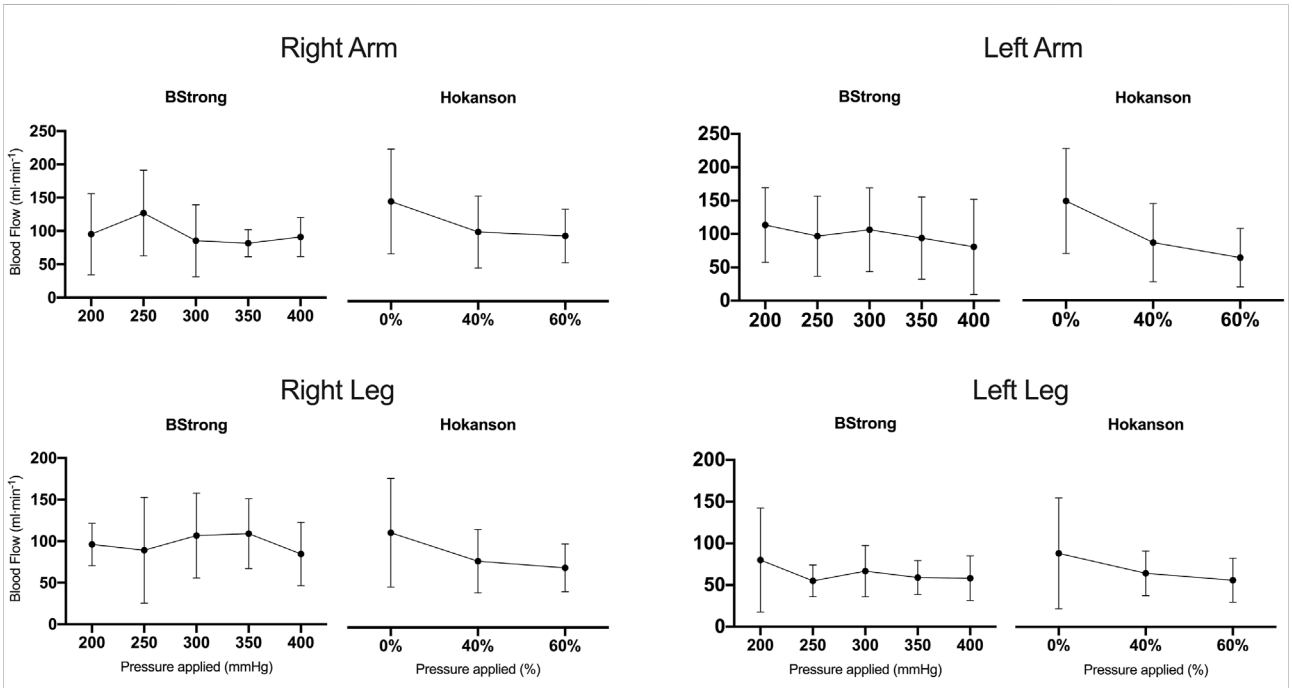

FIGURE 1
Blood flow values (mean ± standard deviations) of right arm, left arm, right leg, and left leg. For both arms and legs, BStrong cuffs were inflated up at 200, 250, 300, 350, and 400 mmHg while Hokanson cuffs were inflated up to 0% (resting values), 40%, and 60% of arterial occlusion pressure.

describe the blood flows that can be expected with different levels of pressure. The recommendations on the occlusion pressure levels are therefore limited to blood flow acute responses and cannot be generalized since we did not investigate either other important criteria (e.g., discomfort) or prolonged physiological adaptations.

BStrong (with 350 and 400mmHg), as well as Hokanson (with 40 and 60% of the AOP), were able to significantly decrease blood flow compared to resting values. However, BStrong, and Hokanson to a lesser extent, struggled to modulate blood flow according to the pressure applied.

BStrong did not significantly decrease blood flow with increasing pressures but showed rather variable blood flows with increasing pressures (Figure 1). Specifically, no significant differences were observed in blood flow between each measured pressure (200, 250, 300, 350, and 400 mmHg). Only the blood flow values with BStrong inflated to a pressure of 350 or 400 mmHg were significantly different from the values at rest (0% AOP). It has been recommended to set BFR pressure as a percentage of the AOP, but it is not possible to do so with BStrong due to its pressure range limit. In regard to blood flow being a targeted variable, the presents results suggest that a pressure equal to or superior to 350 mmHg should be applied in the lower and upper limbs with BStrong.

Hokanson was able to decrease blood flow with increasing levels of pressure, however this was not a linear relationship (Figure 1). Blood flow was significantly decreased between 0 % and 40% of the AOP but not between 40 and 60% of the AOP. Consistent with the results of other studies, no significant difference between pressures ranging from 40 to 80% of the AOP on the legs at rest (Crossley et al., 2020) and between 40 and 60% of the AOP on the upper body (Mouser et al., 2017, 2018) were reported. The current results suggest that pressures as low as 40% of the AOP may offer a comparable restrictive stimulus to higher ones but at more comfortable pressures. This suggestion is reinforced by a study that demonstrated that 8 weeks of BFR training with 40 % vs. 90% of the AOP had similar effects on muscle size and function (Counts et al., 2016).

The profiles of the blood flow changes suggest that Hokanson is a better option for clinical practice while, on the other hand, BStrong seems to be applicable in the practical setting, due to its removable pump and its lower risks associated with the potential wrong use of the cuffs since it is not possible to completely occlude the arteries with this cuff system. These results also highlight that more pressure doesn't always mean less blood flow and that there is variability in the blood flow obtained with BFR. This variability should be considered when practicing BFR. It is hypothesized that several factors may have contributed to this blood flow variability such human error in blood flow measurement, variability in the restrictive stimulus due to the BFR system, duration of occlusion during measurements or duration of rest in-between the measurements.

Cuffs comparison: Individualization, safety, and material

Although it is recommended in the literature to use custom pressures based on a relative percentage of AOP, it cannot be done with BStrong because its pressures range limits the possibility to fully occlude the arteries. Conversely, Hokanson occluded blood flow with its automatic inflation system with an average of 208.5 ± 29.2 (Table 1 for limb by limb averaged pressures). This important difference renders the individualization of the pressures more difficult/not possible with the BStrong cuff system but reduces the risk to its users and thus improves the safety of its use for the public.

The present results showed a significantly higher average blood flow during restriction in the arms than in the legs (p = 0.017) (Figure 1). This could be due to different hemodynamic regulatory mechanisms in response to BFR in the arms vs. the legs. Indeed, another study observed greater deoxygenation and greater blood volume changes in arms vs. legs during repeated sprint tests in hypoxia (Willis et al., 2019). This would suggest greater vascular reactivity of the arms than legs and could explain the present results.

There was a significant difference in blood flows between the left and right sides (p = 0.028). Although not significant, the larger limb's circumferences on the right side (Table 1) could explain this variability (Figure 1). Indeed, the larger the limb, the more pressure in the cuff is needed to reduce blood flow (Loenneke et al., 2012; Jessee et al., 2016). Likewise, when comparing the AOP values obtained in the limbs (Table 1), higher pressure was required to occlude the limbs on the right side than those on the left side. This would highlight the importance of the recommendation that pressure should be established based on the circumference of the limb to ensure safety (Jessee et al., 2016) but also provide a similar stimulus for all participants (Mouser et al., 2018).

The material could likely explain why only 208.5 ± 29.2 mmHg in average leaded to arterial occlusion with Hokanson while higher pressures did not lead to significant difference from resting values (0% of the AOP) with BStrong. Indeed, due to the more rigid nylon character, Hokanson cuffs are stretched less easily than elastic cuffs and therefore compress more soft tissues. Therefore, cuffs constructed of more rigid materials would occlude the limbs with less pressure than more elastic cuffs. Similarly, Buckner et al. (2017) found resting AOP higher with nylon cuffs (Hokanson, Bellevue, WA, United States) than with elastic cuffs (Kaatsu Master, Tokyo, Japan) of the same width in the upper body while Loenneke et al. (2013) observed no significant difference between elastic (Kaatsu Master, Tokyo, Japan) vs. nylon (Hokanson, Bellevue, WA, United States) cuffs of similar size in the lower body. These opposite results suggest that there may even be differences between elastic cuffs. It is therefore important to consider the type of cuff used, as well as its width (Mattocks et al., 2018; Patterson et al., 2019) when practicing BFR, because it may lead to a completely different restriction stimulus.

Limitations

The small sample size of this study (n = 11) related to the available resources underlines the need for further investigation. It should also be noted that the measurements were taken while resting in a seated position. The use of this information relative to seated rest must be interpreted with caution when applying to participants during exercise. Exercise, causing increased blood flow to the working muscles, is likely to need higher pressure to restrict comparably arterial flow. Despite these limitations, the present results provide an important adjunct to the BFR literature, by analyzing the differences between two cuff systems of similar size but different materials and pointing up the variability of blood flow restriction.

Practical applications

These results underline first the variability in blood flow that can occur when applying pressure with different BFR cuffs materials. This variability should be kept in mind when practicing BFR. The users should therefore not expect a linear decrease in blood flow when increasing the pressure.

Current results suggest that a pressure ≥ to 350 mmHg should be applied with BStrong and that pressure as low as 40% of the AOP can be applied to achieve a BFR comparable to higher (60%) and less comfortable pressures with Hokanson. Despite the importance of restrictive pressure application, the effectiveness of BFR training also depends on the protocol chosen. The practitioner must adjust training variables (load, intensity, volume) to achieve muscle changes (Patterson et al., 2019). In addition, it was suggested that the AOP increases with exercise so it should be taken into account when trying to set an optimal relative pressure (Barnett et al., 2016).

BStrong did not decrease blood flow with increasing pressures, it seems therefore not possible to modulate blood flow with BStrong. On the other hand, Hokanson decreased blood flow with increasing pressures, but not significantly, it seems for this reason roughly possible to modulate blood flow with Hokanson. It is also worth mentioning that the recommended BStrong pressure levels in the current study are even superior to the AOP obtained with Hokanson which could increase discomfort. Beyond these results, BStrong has practical considerations (e.g., training and/or rehabilitation) as the pump can be removed from the valve once inflated which allows the users to move freely instead of performing exercise while connected to an inflation system.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of the Canton Vaud. The patients/participants provided their written informed consent to participate in this study.

Author contributions

SW, GM, and AC contributed to the conception and design of the study. AC and SW collected the data and organized the database. AC, SW, and TC performed the data analysis. AC, SW, and TC performed the statistical analysis. TC wrote the first draft of the manuscript. All authors contributed to the manuscript revision, and read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A call to action for blood flow restriction training in older adults with or susceptible to sarcopenia: A systematic review and meta-analysis

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Background: The extent to which exercise training with blood flow restriction (BFR) improves functional performance (FP) in people with sarcopenia remains unclear. We performed a comprehensive search of BFR training in subjects with sarcopenia or susceptible to sarcopenia hoping to perform a systematic review and meta-analysis on the effects of BFR on FP in older adults without medical disorders, but with or susceptible to sarcopenia.

Methods: PubMed and the Cochrane library were searched through February 2022. Inclusion criteria were: 1) the study examined older adults (>55 years of age) with or susceptible to sarcopenia and free of overt acute or chronic diseases, 2) there was a random allocation of participants to BFR and active control groups, 3) BFR was the sole intervention difference between the groups, and 4) the study provided post-intervention measures of skeletal muscle and physical function which were either the same or comparable to those included in the revised European Working Group on Sarcopenia in Older People (EWGSOP) diagnostic algorithm.

Results: No studies of BFR training in individuals with sarcopenia were found and no study included individuals with FP values below the EWGSOP criteria. However, four studies of BFR training in older adults in which FP was examined were found. BFR training significantly improved the timed up and go (MD = −0.46, z = 2.43, p = 0.02), 30-s chair stand (MD = 2.78, z = 3.72, $p < 0.001$), and knee extension strength (standardized MD = 0.5, z = 2.3, p = 0.02) in older adults.

Conclusion: No studies of BFR exercise appear to have been performed in patients with or suspected sarcopenia based on latest diagnostic criteria. Despite the absence of such studies, BFR training was found to significantly improve the TUG, 30-s chair stand, and knee extension strength in older adults. Studies examining the effects of BFR in subjects below EWGSOP cut-off points are needed.

KEYWORDS

blood flow restriction, vascular occlusion training, aged, elderly, sarcopenia, skeletal muscle function, physical function, functional performance

Introduction

Sarcopenia is defined as a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes, including falls, fractures, physical disability, and mortality for which methods to identify and manage it are extremely important and warranted (Cruz-Jentoft et al., 2019). The Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls (SARC-F) questionnaire provides a rapid assessment of probable sarcopenia using the above five criteria, each of which are scored from a minimum to maximum level of 0–2 resulting in a maximum total SARC-F score of 10 criteria, with scores ≥4 highlighting the need for further testing (Cruz-Jentoft et al., 2019). Furthermore, the revised European Working Group on Sarcopenia in Older People (EWGSOP) consensus on the definition and diagnosis of sarcopenia published in 2019 provides a framework to classify sarcopenia and the impairments associated with it by identifying cut-points for specific tests and measures (Table 1). (Cruz-Jentoft et al., 2019) Examples of such tests and measures include grip strength, chair stand ability, muscle quantity, and functional performance using gait speed, the short physical performance battery (SPPB), the timed up and go (TUG), and 400-m walk tests. Thus, SARC-F scores and outcomes from the above tests and measures can be used to identify the presence of sarcopenia or susceptibility (likely to be influenced) by sarcopenia.

Management of sarcopenia includes a variety of methods with physical activity, exercise training, and nutritional supplementation consistently identified as effective interventions for sarcopenia. (Negm et al., 2022). Resistance training alone or combined with aerobic exercise appears to be the most effective intervention for sarcopenia (Burton and Sumukadas, 2010; Negm et al., 2022). However, resistance training or aerobic exercise performed at the higher intensities required to elicit optimal physiological adaptations may be difficult for older people with or susceptible to sarcopenia. Furthermore, resistance training and aerobic exercise performed at higher intensities may be associated with a greater risk of injury in a frail population of subjects like many individuals with sarcopenia (Skelton and Mavroeidi, 2018; Di Monaco et al., 2020). Thus, low-load resistance training or aerobic exercise with blood flow restriction (BFR) has been suggested as a potential method to improve skeletal muscle strength and decrease the risk of injury in older people with sarcopenia, which may improve adherence to exercise (Hughes et al., 2017; Beckwée et al., 2019; Conceição and Ugrinowitsch, 2019). In fact, a previous systematic review and meta-analysis of BFR training identified 13 studies in which older adults susceptible to sarcopenia underwent BFR training, with eight of the 13 studies suitable for meta-analysis. The results found a moderate effect (Hedges' g = 0.523) of low-load BFR training compared to training with the same load without BFR on improving skeletal muscle strength (Hughes et al., 2017). Thus, BFR training may be a practical adjunct to increase strength and potentially improve recovery from strengthening exercise. However, no functional performance (FP) measures were examined in the above meta-analysis, which may provide insight into the degree of susceptibility to sarcopenia and effects of BFR training on FP.

However, a relatively recent systematic review of chronic BFR exercise found that data from 13 studies with a total of 332 participants improved a variety of FP measures with the 30 s sit-to-stand and TUG tests being most improved (Clarkson et al., 2019). In this systematic review, studies of individuals with a variety of different medical conditions were included such as body myositis, end-stage kidney disease, knee injury and knee osteoarthritis. Although individuals with sarcopenia may have one or more of the above disorders, it is important to examine the literature in

TABLE 1 European working group on sarcopenia in older people cut-off points. (Cruz-Jentoft et al., 2019).

Test	Cut-off points for men	Cut-off points for women	References
Grip strength (kg)	<27	<16	Dodds et al. (2014)
Chair stand (sec)	>15 for five rises	—	Cesari et al. (2009)
Gait speed (m/sec)	≤0.8	—	(Studenski et al., 2011; Cruz-Jentoft et al., 2019)
SPPB (0–12 points)	≤8 points	≤8 points	(Guralnik et al., 1995; Pavasini et al., 2016)
TUG (sec)	≥20	≥20	Bischoff et al. (2003)
400 m walk test	Unable to complete or ≥6 min to complete	Unable to complete or ≥6 min to complete	Newman et al. (2006)

Abbreviations: SPPB, short physical performance battery; TUG, timed up and go.

subjects without medical disorders as this may confound the effect of BFR training on sarcopenia. Additionally, we sought to examine the available BFR literature to better identify the degree of susceptibility or presence of sarcopenia using SARC-F and EWGSOP outcomes. Finally, to fully capture the effects of BFR training in subjects with or susceptible to sarcopenia, we examined previous BFR literature in which BFR training was compared to a non-BFR equivalent exercise training group (i.e., active control group) rather than inactive control or different intensity BFR exercise groups. Thus, the purpose of this study was to perform a systematic review of BFR training in subjects with sarcopenia or susceptible to sarcopenia and to conduct a meta-analysis on the effects of BFR on FP in older adults without medical disorders, but with or susceptible to sarcopenia based on SARC-F and EWGSOP outcomes in whom BFR training was compared to a non-BFR equivalent exercise training group.

Methods

Search strategy and data sources

A comprehensive literature review was performed in PubMed and the Cochrane library through February 2022. Supplementary Appendix S1 presents the complete search strategy which was conducted in English and included a mix of terms for the key concepts blood flow restriction, sarcopenia, skeletal muscle and physical function. The reference list of eligible studies was also screened to identify other potentially relevant publications.

Study selection

A study had to meet the following criteria to be included in the meta-analysis: 1) the study was conducted in older adults (>55 years of age) with or susceptible to sarcopenia and free of overt acute or chronic diseases (since such individuals would likely have poorer FP measures and a greater degree of sarcopenia in whom a less realistic effect of BFR training on FP may result), 2) there was random allocation of study participants to BFR and active control groups, 3) BFR was the sole intervention difference between the groups, and 4) the study provided post-intervention outcome measures of skeletal muscle and physical function, which were either the same or comparable to those included in the revised European Working Group on Sarcopenia in Older People (EWGSOP) diagnostic algorithm. (Cruz-Jentoft et al., 2019). Any studies not meeting these criteria were excluded. Studies were only considered for eligibility if they had been peer reviewed and published prior to the search.

Data extraction and quality assessment

All included studies were assessed for methodological quality and reporting characteristics using the TESTEX tool to assist with the interpretation of results (Smart et al., 2015). Study quality was assessed *via* the Cohen's kappa, which revealed that study quality was in complete agreement (k = 1) between coders. Two authors independently read and coded each study for descriptive information including: 1) publication year, 2) gender (1 = only males, 2 = only females, 3 = mixed) and 3) age of the participants in the studies. For both BFR and standard training protocols, the mode of exercise performed and exercise training intensity were coded (1 = walking/treadmill protocol, 2 = resistance training protocol, 3 = other (e.g., functional training); and 1 = low to moderate intensity, 2 = high intensity, respectively). Means, standard deviations, and sample size of post-intervention data for the following outcome measures were obtained and recorded as continuous variables: Timed Up and Go, in seconds taken to complete the test activity; 30-Second Chair Stand, in number of repetitions performed; 6-Minute Walk Test, in distance walked in meters; and the Romberg Test, in seconds the patient was able to stand with eyes closed. Means and standard deviations of post-intervention knee extension strength measures were also recorded as continuous variables when available for supplementary pooled analyses carried out for discussion purposes. Cohen's kappa determined that the coders were in complete agreement (k = 1). Pearson correlation analysis also demonstrated complete consistency among raters (r = 1).

Data synthesis and analysis

RevMan, version 5.3 (Cochrane, London, United Kingdom) was used for data analyses. Overall effect estimates were calculated using random-effects models with inverse variance weighting to allow us to address any existing heterogeneity. Either standardized or unstandardized mean differences were computed for each pooled analysis as appropriate along with I^2 information, representing the percentage of the variability in effect estimates due to heterogeneity. 95% confidence intervals of each study were also calculated. Z scores provided the overall effect of intervention versus control with statistical significance set at a p-value < 0.05.

Results

No studies of BFR training in individuals with sarcopenia meeting our inclusion criteria could be found and no study included individuals with mean ± SD scores (or individual scores when available) of FP below the EWGSOP criteria listed in

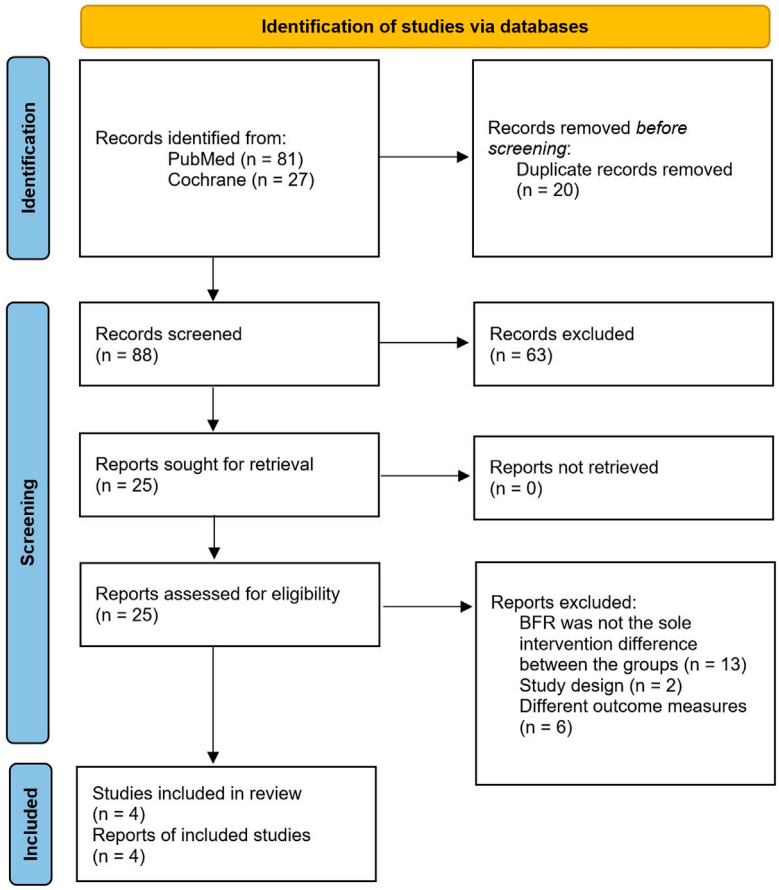

FIGURE 1
Flow diagram of study selection.

Table 1. Also, no studies of BFR training in which SARC-F scores were reported could be found.

However, four studies of BFR training in older adults in which FP was examined were found and included the following FP measures: TUG (n = 4), (Ozaki et al., 2011; Clarkson et al., 2017; Bigdeli et al., 2020; Kargaran et al., 2021) 30-s chair stand test (n = 3), (Ozaki et al., 2011; Clarkson et al., 2017; Kargaran et al., 2021) 6-min walk test (6MWT; n = 2), (Clarkson et al., 2017; Kargaran et al., 2021) Romberg balance test (n = 2), (Bigdeli et al., 2020; Kargaran et al., 2021) and knee extension strength (n = 3) (Ozaki et al., 2011; Bigdeli et al., 2020; Kargaran et al., 2021). A flow diagram of the studies retrieved for the meta-analysis is presented in Figure 1, as per PRISMA reporting guidelines (Page et al., 2021). Table 2 provides an overview of these four studies. The quality of the studies using the TESTEX assessment tool is shown in Table 3, which found that two of the studies had excellent quality and very good reporting characteristics Bigdeli et al. (2020), Kargaran et al. (2021) with the other two studies having moderate to good quality and reporting Clarkson et al. (2017), Ozaki et al. (2011). Risk of bias assessment as per Cochrane Collaboration guidelines is presented in Figure 2.

Two of the studies included only older women, one study included only older men, and one study included both men and women who were older. The age range of subjects in the studies was from 62.9 ± 3.1 to 70 ± 7 years (Ozaki et al., 2011; Clarkson et al., 2017; Bigdeli et al., 2020; Kargaran et al., 2021). The number of subjects in the BFR and non-BFR groups was relatively well matched, with two studies having the same number of subjects and the other two studies differing by one and two subjects per group. The four studies included a total of 73 individuals of whom 57.5% were women. (Ozaki et al., 2011; Clarkson et al., 2017; Bigdeli et al., 2020; Kargaran et al., 2021).

Treadmill walking with and without BFR was performed in two of the studies at the same intensity (45% of HRR) (Ozaki et al., 2011; Kargaran et al., 2021) with one of the studies imposing cognitive-tasks while walking (Kargaran et al., 2021). The study imposing cognitive tasks while walking was performed for 20 min, 3x/week for 8 weeks, (Kargaran et al., 2021) and the other treadmill walking study was also performed for 20 min, but

TABLE 2 Overall characteristics of participants per study.

Author (Year)	Population (mean age)	BFR group	Non-BFR equivalent exercise group	Baseline BFR group FP measures and mean score	Baseline Non-BFR equivalent ex. Group FP measures and mean score
Ozaki et al. (2011)[8]	Older women (66 ± 1 year)	*n* = 10; 20 min of TM walking at 45% HRR, 4x/week for 10 weeks with Kaatsu-Master cuffs placed on the most proximal portion of each leg at AOP of 140–200 mm Hg	*N* = 8; 20 min of TM walking at 45% HRR without BFR, 4x/week for 10 weeks	TUG = 5.0 s 30 s chair stand = 23 knee ext. Torque (nm) Iso = 120 30°/sec = 103 180°/sec = 66	TUG = 4.9 s 30 s chair stand = 24 knee ext. Torque (nm) Iso = 120 30°/sec = 98 180°/sec = 65
Bigdeli et al. (2020)[11]	Older men (67.7 ± 5.8 years)	*n* = 10; 2–4 sets of 10 reps at 11 FT stations alternating between UE and LE exercise performed at 25%–35% of 1RM with cuffs placed on the proximal extremities at AOP of 50%–70%, 3x/week for 6 weeks with cuffs deflated during 1 min rest periods between sets	*n* = 10; 2–4 sets of 10 reps at 11 FT stations alternating between UE and LE exercise performed at 25%–35% of 1RM without BFR	TUG = 10 s Romberg = 5.5 knee ext. Strength (kg) = 31.7	TUG = 10.9 s Romberg = 4.6 knee ext. Strength (kg) = 31.0
Kargaran et al. (2021)[9]	Older women (62.9 ± 3.1 yr)	*n* = 8; 20 min of TM walking, 3x/week for 8 weeks at 45% HRR while performing several cognitive tasks with cuffs placed on the proximal LE at AOP of 50% which was increased by 10% every 2 weeks	*N* = 8; 20 min of TM walking, 3x/week for 8 weeks at 45% HRR while performing several cognitive tasks without BFR	TUG = 6.4 s 30 s chair stand = 19.7 6MWT = 530 m Romberg = 6.5 knee ext. Strength (kg) = 19.8	TUG = 7.2 s 30 s chair stand = 18.4 6MWT = 479 m Romberg = 7.4 knee ext. Strength (kg) = 19.6
Clarkson et al. (2017)[10]	Sedentary older men and women (BFR and non-BFR group age was 69 ± 6 and 70 ± 7 years, respectively)	*n* = 10 (6 men, 4 women); 10 min of walking at 4 km h^{-1} around a 667 m field circuit 4x/week for 6 weeks with cuffs placed on the most proximal portion of each leg at AOP of 60%	*n* = 9 (5 men, 4 women); 10 min of walking at 4 km h^{-1} around a 667 m field circuit 4x/week for 6 weeks	TUG = 6.6 s 30 s chair stand = 14.5 6MWT = 505 m	TUG = 6.75 s 30 s chair stand = 14.9 6MWT = 528 m

Abbreviations: 1-RM, One-repetition maximum; 6MWT, Six-minute walk test; AOP, arterial occlusion pressure; BFR, blood flow restriction; FP, functional performance; FT, functional training; HRR, heart rate reserve; LE, lower extremity; TM, treadmill; TUG, timed up and go; UE, upper extremity.

TABLE 3 TESTEX assessment of the quality and reporting of included randomized controlled trials.

	Study quality criterion						Study reporting criterion											
Study	1	2	3	4	5	Total	6a	6b	6c	7	8a	8b	9	10	11	12	Total	Overall Total
Bigdeli et al. (2020)	1	1	1	1	1	5	1	0	0	1	1	1	1	0	1	1	7	12
Clarkson et al. (2017)	1	1	0	1	0	3	1	0	0	1	1	1	1	1	0	1	7	10
Kargaran et al. (2021)	1	1	1	1	1	5	1	0	1	1	1	1	1	0	0	1	7	12
Ozaki et al. (2011)	1	1	0	1	1	4	1	0	0	1	1	1	1	0	0	1	6	10

with a slightly greater frequency and duration (4x/week for 10 weeks) (Ozaki et al., 2011). A third study also used walking as the mode of exercise with and without BFR which was done around a 667 m field circuit for 10 min at 4 km h^{-1}, 4x/week for 6 weeks (Clarkson et al., 2017). The fourth study performed functional training (FT) exercises with and without BFR, which included 2–4 sets of 10 reps at 11 FT stations alternating between UE and LE exercise performed at 25%–35% of 1RM. (Bigdeli et al., 2020).

The only EWGSOP FP measure for sarcopenia that was reported in the included studies was the TUG (Cruz-Jentoft et al., 2019). None of the participants enrolled in the four studies included in this meta-analysis approached the cut-off score of ≥20 s with participants in three of four studies completing

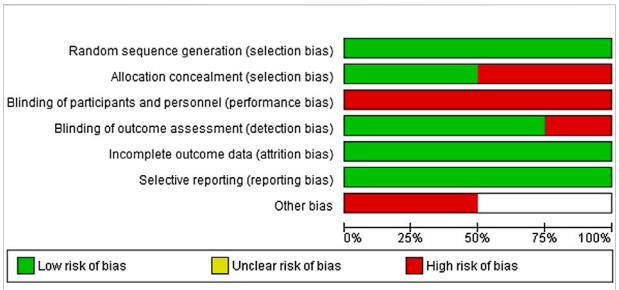

FIGURE 2
Analysis of risk of bias according to Cochrane Collaboration guidelines.

the TUG in less than 10 s, (Ozaki et al., 2011; Clarkson et al., 2017; Kargaran et al., 2021) and in the other study the BFR and non-BFR group participants completed the TUG in 10 and 10.9 s, respectively (Bigdeli et al., 2020). No reports of adverse events during or after BFR or non-BFR equivalent exercise were found in any of the studies (Ozaki et al., 2011; Clarkson et al., 2017; Bigdeli et al., 2020; Kargaran et al., 2021).

The Forest Plots and results of the meta-analyses for the TUG, 30-s chair stand, 6MWT, Romberg balance test, and knee extension strength are shown in Figure 3, in which BFR training was found to significantly improve the TUG, 30-s chair stand, and knee extension strength in older adults. BFR training had no significant effect on the 6MWT or Romberg balance test, but the results favored BFR training compared to a non-BFR equivalent exercise training group (Figure 3). The degree of heterogeneity reflected by the I^2 values in the 30-s chair stand test, knee extension strength, and Romberg balance test was low (16%, 0%, and 0%, respectively), while that of the TUG was modest (58%), and the 6MWT high (71%).

Discussion

The results of a comprehensive search for studies examining the effects of BFR training in older adults with or susceptible to sarcopenia using SARC-F and EWGSOP outcomes was disappointing. No study of BFR training could be found using the SARC-F criteria and the only EWGSOP FP measure for sarcopenia that could be used was the TUG. None of the participants enrolled in the four studies included in this meta-analysis approached the cut-off score of ≥20 s. In view of the above results, studies examining the effects of BFR on FP in subjects with sarcopenia are needed. Nonetheless, this is the first meta-analysis to examine the effects of BFR training on FP in older adults without medical disorders and found that no studies of BFR appear to have been performed in patients with sarcopenia or suspected sarcopenia based on SARC-F and EWGSOP outcomes.

Despite the absence of studies examining the effects of BFR exercise in patients with or susceptible to sarcopenia, BFR training was found to significantly improve the TUG, 30-s chair stand, and knee extension strength compared to exercise training without BFR in older adults. These are important findings in regards to the FP of older adults and likely to the FP of individuals with sarcopenia, who in view of the EWGSOP criteria, will have poorer baseline FP, (Cruz-Jentoft et al., 2019) and may have even greater improvements in these and other FP measures. Also, although knee extension strength may not be a true FP measure, it is significantly correlated to a variety of FP measures, including gait speed, chair stand, and balance (Cai et al., 2022). Furthermore, isokinetic knee extension and flexion strength appear to have the ability to identify sarcopenia (Steffl and Stastny, 2020; kis et al., 2022). Several review articles have presented the rationale for BFR being an effective non-pharmacological treatment of sarcopenia, (Beckwée et al., 2019; Conceição and Ugrinowitsch, 2019) but research focused on the effects of BFR training in patients with sarcopenia is lacking and thus identifies the need for future investigation given the results of this study. Thus, a call for action for research and research funding to support and perform studies on BFR training in subjects with sarcopenia is desperately needed in view of the aging population in the United States (2020 Profile of Older Americans, 2021; von Elm et al., 2008; Bischoff et al., 2003) and the globe (World Population Ageing 2019: Highlights, 2019; Newman et al., 2006) as well as the improvements in FP observed in this study. Future research must ensure to implement BFR according to current understanding of optimal parameters, such as training being individualized to limb occlusion pressure, appropriate loading and progression (Patterson et al., 2019). While research in individuals with sarcopenia is warranted, it is important that further investigations follow best practice as methodological heterogeneity will limit the formulation of accurate and informative conclusions on training effectiveness and safety.

One case report of BFR training in a 91-year old sedentary man diagnosed with sarcopenia [appendicular skeletal muscle mass (ASM) of 7.10 kg/m^2) was found in which the subject presented with exhaustion, lower-limb weakness, hypertension, and a history of multiple falls (Lopes et al., 2019). Three months of low-intensity upper and lower extremity resistance training (3 sets of 10 repetitions at 30% of one RM for elbow flexion and extension, knee extension, and leg press) were initially performed which was followed by 1 month of inactivity during, which the subject was asked to maintain instrumental activities of daily living (ADLs) and avoid any changes in his routine. Following the 1 month of inactivity, the subject performed 8 weeks of BFR training at the same intensity while exercising with the same number of sets, repetitions, and muscle groups (Lopes et al., 2019). Protein supplementation was provided to the subject after low-intensity resistance training with and without BFR

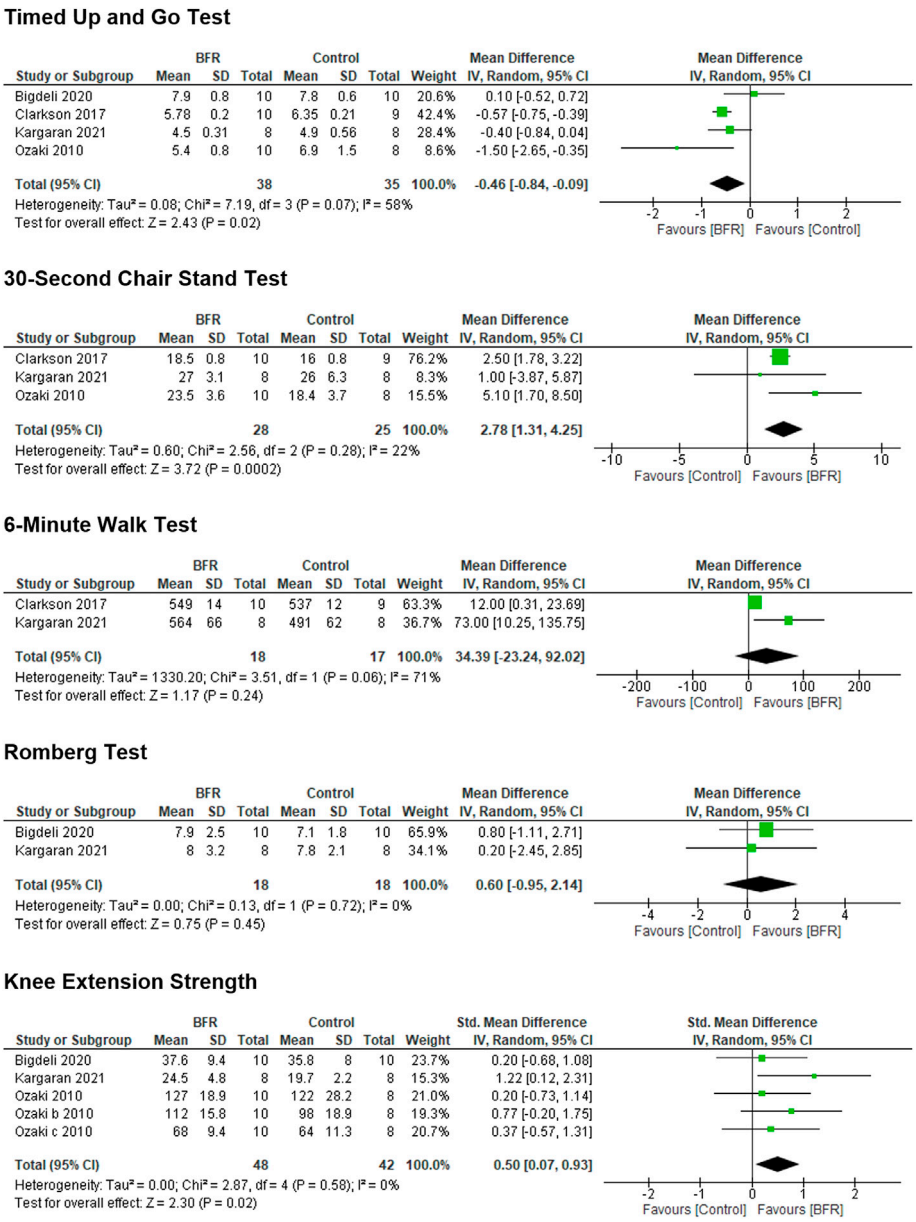

FIGURE 3
Forest plots showing the effects of blood flow restriction training on different functional performance measures in older adults.

(Lopes et al., 2019). The results of low-intensity resistance training with BFR on body composition, sarcopenia cut-points, and strength were greater than that observed with low-intensity resistance training without BFR. For example, low-intensity resistance training without BFR resulted in 2.7% decreases in ASM and total skeletal muscle mass (SMM), but low-intensity resistance training with BFR produced 2.3 and 2.1% increases in these same respective measures (Lopes et al., 2019). Handgrip strength was found to decrease 3.4% after low-intensity resistance training without BFR, but increased 17.9% after low-intensity resistance training with BFR (Lopes et al., 2019). Furthermore, isokinetic knee extension peak torque, total work, and work fatigue decreased after low-intensity resistance training without BFR (8.8%–20.4%), but increased after low-intensity resistance training with BFR (1.5%–27.5%). Additionally, interleukin-6 (IL-6) and insulin-like growth factor-1 (IGF-1) were improved, but endothelin-1 and oxidative stress increased with less endothelial vasoreactivity after low-intensity resistance training with BFR (Lopes et al., 2019). In view of the above findings in a single case subject, BFR training has the

potential to improve key pathophysiological manifestations of sarcopenia, but further investigation of its effects on oxidative stress and endothelial function is needed.

Two of the studies included in this meta-analysis examined blood markers indirectly related to oxidative stress and endothelial function and directly related to neuromuscular activity (Bigdeli et al., 2020; Kargaran et al. (2021) examined the effects of dual-task treadmill walking with and without BFR on brain-derived neurotrophic factor (BDNF), procollagen III N-terminal peptide (P3NP), and C-terminal Agrin (CAF), and found significant increases in BDNF after 8 weeks in both dual-task walking with and without BFR which was not observed in the control group that performed everyday activities, but without dual-tasks. (Kargaran et al., 2021) Furthermore, the CAF concentration in the dual-task walking with BFR group was significantly lower than that observed in the dual-task walking without BFR or control groups. Finally, only the dual-task walking group was found to have a significant increase in the level of P3NP after the 8-weeks study period (Kargaran et al., 2021). The increase in P3NP is suggestive of a greater anabolic response while the decrease in CAF suggests less neuromuscular junction remodeling, degradation, and muscle wasting. Bigdeli et al. (2020) also examined CAF and P3NP levels before and after functional training with and without BFR and found results similar to Kargaran et al. (2021) in that CAF levels were lower after 6 weeks of functional training with BFR than after functional training without BFR, and were significantly lower than levels in a control group which maintained ADLs (Bigdeli et al., 2020). Although Bigdeli found no significant difference in P3NP levels among groups, the decrease in P3NP observed in all groups was less in the functional training with BFR group (Bigdeli et al., 2020). In view of the above, we performed an additional meta-analysis on the CAF and P3NP results from these two studies and found a significant decrease in CAF after exercise with BFR compared to exercise without BFR [Std. Mean Diff = −0.76, (95% CI: 1.44, −0.07); Z = 2.17; p = 0.03; I^2 = 0%] and no effect on P3NP [Std. Mean Diff = 0.14, (95% CI: 0.90, 1.19); Z = 0.27; p = 0.79; I^2 = 58%] (Bigdeli et al., 2020; Kargaran et al., 2021). Thus, in view of the above results, BFR exercise has the potential to decrease CAF levels suggesting less neuromuscular junction remodeling, degradation, and muscle wasting all of which would be beneficial for the FP of subjects with sarcopenia.

One final note related to the above blood markers and FP is that Bigdeli et al. (2020) found significant negative correlations between the level of CAF and knee extension, chest press, and static balance and significant positive correlations between the level of P3NP and chest press (Bigdeli et al., 2020). Similarly, Kargaran et al. (2021) found a significant negative correlation between CAF level and leg skeletal muscle quality and a significant positive correlation between P3NP level and leg skeletal muscle quality only in the BFR exercise group (Kargaran et al., 2021). Kargaran also found that BDNF level was significantly correlated to the Mini-Mental State Examination in all groups. Although these findings are encouraging for patients with sarcopenia, further examination of BFR training on the above blood markers and their relationship to FP and cognition in older adults with sarcopenia is needed.

Several limitations of this meta-analysis with systematic review exist, including a small number of studies and number of subjects included in the analyses as well as a small number of studies examining the level of CAF and P3NP. Although the inclusion of only studies in which healthy subjects without medical disorders were enrolled and BFR training was compared to a non-BFR equivalent exercise training group limited the number of studies included in our analyses, we believe it is a strength of the study. The finding that no studies of BFR exercise in subjects with sarcopenia or suspected sarcopenia exist is worrisome and identifies the need for research focus and funding to examine the effects of BFR exercise on skeletal muscle strength, quantity, quality, and FP as outlined by the EWGSOP (Cruz-Jentoft et al., 2019). The examination of BFR exercise compared to a non-BFR equivalent exercise in subjects below the EWGSOP cut-off points is needed and in view of the results of this meta-analysis and systematic review may identify an important non-pharmacologic intervention for sarcopenia.

Conclusion

No studies of BFR exercise appear to have been performed in patients with sarcopenia or suspected sarcopenia based on SARC-F and EWGSOP outcomes. However, despite the absence of studies examining the effects of BFR exercise in patients with or susceptible to sarcopenia, BFR training was found to significantly improve the TUG, 30-s chair stand, and knee extension strength in older adults making BFR exercise a practical adjunct in the management of subjects with sarcopenia. The only EWGSOP FP cut-off point for sarcopenia that could be used was the TUG and one of the participants enrolled in the four studies included in this meta-analysis approached the EWGSOP cut-off score of ≥20 s with participants in three of four studies completing the TUG in less than 10 s, (Ozaki et al., 2011; Clarkson et al., 2017; Kargaran et al., 2021) and in the other study, the BFR and non-BFR group participants completed the TUG in 10 and 10.9 s, respectively (Bigdeli et al., 2020). In view of the above results, studies examining the effects of BFR on FP as well as skeletal muscle strength, quantity, and quality as outlined in the EWGSOP consensus in subjects with sarcopenia are needed (Cruz-Jentoft et al., 2019). Furthermore, further investigation of isokinetic testing appears warranted in view of the significant improvement in knee extension strength

observed in this study as well as other literature highlighting its potential role in identifying sarcopenia. (Steffl and Stastny, 2020; kis et al., 2022). The significant improvements in FP of older adults observed in this study is important especially in view of the EWGSOP criteria in which older adults with sarcopenia are likely to have poorer baseline FP with the potential for even greater improvements in these and other FP measures.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

LC and MF contributed to conception and design of the study. LC, MF, BA, GF, EH, JO, and LH contributed substantially to data analysis and interpretation, and the writing of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

JO is affiliated with Owens Recovery Science. He is a paid consultant/distributor for Delfi Medical Innovations, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2022.924614/full#supplementary-material

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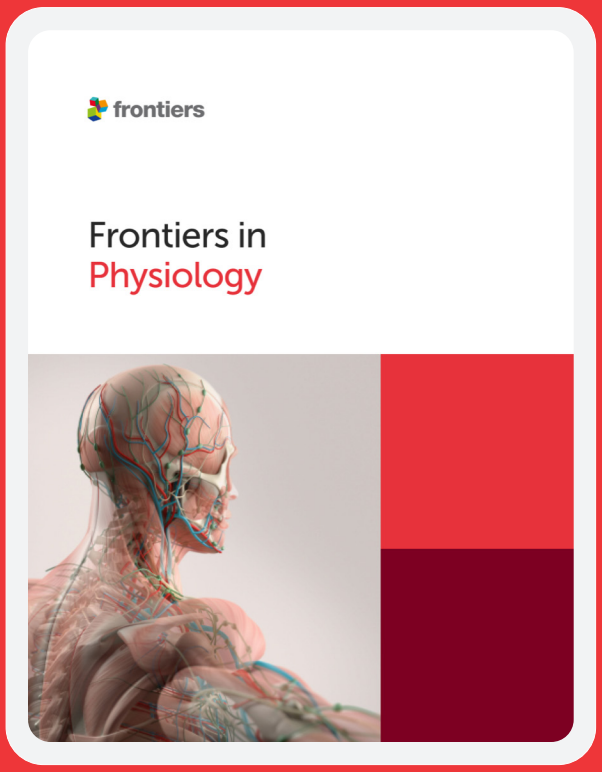

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