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Effect of Blood Flow Restriction Training on Physiological Outcomes in Healthy Athletes: a Systematic Review and Meta-Analysis

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SUMMARY

Background. Blood flow restriction (BFR) training is gaining increasing attention in the scientific community. Studies using exercise combined with blood flow restriction have shown muscle strength and size improvement. In fact, the main feature of BFR training is that can elicit muscle hypertrophy and strength adaptations using light external loads (20-30% one repetition maximum, 1RM) comparable to what is typically seen following high-load (HL) training programs with 70-85% 1RM. This specific training has applications for individuals who may not be able to tolerate the mechanical stresses associated with higher loads, such as the elderly or injured; thus, several investigations have focused on implementing BFR exercise within older and clinical populations. However, the effects of this kind of technique in healthy athletes are not clear in scientific literature. The purpose of this study is to conduct a systematic review with meta-analysis to evaluate the qualitative and quantitative results of blood flow restriction training in healthy athletes.

Methods. PRISMA guidelines were used to carry out the systematic review and meta-analysis. Three electronic databases were searched: MEDLINE, PEDro, and the Cochrane Library. Papers included in the study have the following characteristics: a) a randomized controlled trial or clinical trial design of research, b) studies investigating physiological effects of BFR training in healthy athletes and c) published in English. The approach to data extraction was chosen on the basis of the Cochrane Methods. Studies quality and risk of bias of the clinical trials included were evaluated according to a Jadad score and through meta-analysis.

Results. After the elimination of duplicates, 164 records were screened. Among these, 14 studies were included in the systematic review. Seven of these were involved in the meta-analysis. From the qualitative analysis, a larger number of studies were found with a low level of quality.

Conclusions. The application of BFR positively influences muscular adaptations compared with exercise under normal blood-flow conditions, in terms of increased VO_2 max, higher strength increase, and muscles adaptations. Thus, BFR provides a feasible, promising, and beneficial complementary training stimuli when used in a controlled environment supervised by trained and experienced personnel.

KEY WORDS

Blood flow restriction; katsu; athletes; BFR; sports; Exercise Training.

INTRODUCTION

Athletes who compete, although in different types of sports, usually they use strength and resistance training to enhance sport-specific muscular development and subsequent performance (1-4). Historically, heavy exercise loads of approximately 70% of an individual's one repetition maximum (1RM) have been deemed necessary to elicit muscle hypertrophy and strength gains (5). The American College of Sports Medicine (ACSM) recommends loads of 60%-70% of the maximum load a person can lift (1 repetition maxi-

mum (1RM)) to develop muscle strength, and 70%-85% 1RM to produce muscle hypertrophy (6). In recent years, research has demonstrated that augmentation of low-load resistance training with Blood Flow Restriction (BFR), also known as Kaatsu training (7), to the active musculature can produce significant hypertrophy and strength gains (8-11), using loads as low as 30% 1RM (7). BFR training has been found to yield hypertrophy responses comparable to that observed with heavy load resistance training (12).
The BFR in such exercise protocols is typically achieved by restricting blood flow to the muscle with the application of external pressure via a tourniquet (13), pressurized cuff (14), or elastic banding (15) that is applied over the proximal portion of the upper or lower extremities. It has been suggested that the external pressure applied is sufficient to maintain arterial inflow whilst occluding venous outflow of blood distal to the occlusion site (16), although here, it is difficult to envisage sufficient arterial inflow, since such restricted venous return is likely to reduce inflow of blood to the muscle.
The cuff restricts arterial blood flow and venous return, causing a greater rate of muscle fatigue than normal conditions (17). This reduced blood flow is thought to induce an ischemic/hypoxic environment that enhances the training effect in exercising muscle, leading to increased muscle mass and strength (9, 18-21). Despite the fact that the robust effects of BFR resistance training in producing muscle hypertrophy have previously been documented by numerous studies (16, 18-30), the underlying mechanisms responsible for such effects remain poorly understood.
Some of the proposed mechanisms involved in the hypertrophic response from low-load BFR training include: elevated systemic hormone production (27, 28), cell swelling (29, 30), increased production of reactive oxygen species (ROS) (16, 24, 31), increased recruitment of fast-twitch muscle fibres (18, 32-34), intramuscular anabolic/anti-catabolic signaling (22, 35, 36), reactive hyperemia (37). In a very recent study, authors using coefficient of variation of force (CVf) and surface electromyographic signal (sEMG) suggest peculiar pattern of neuromuscular fatigue (38).
Additionally, while both low-load BFR training and traditional high-load training may work through alternate mechanisms, they appear to both be reliant on the activation of the mechanistic target of rapamycin (mTOR) pathway, as evident by the blunted protein synthetic response when rapamycin, an mTOR suppressor, is administered (39, 40). Despite the low level of mechanical tension associated with BFR resistance training, both mechanical tension and metabolic stress are primary factors of muscle hypertrophy, it seems reasonable to argue that metabolic stress plays the dominant role (41).
However, at present these are mainly hypothetical and theoretical-based associations.
The advantage of low loads and thus reduced mechanical stress for joints and bones (12) is of particular interest for populations who are not capable of lifting near-maximum loads or for whom high loads may be contraindicated, such as in clinical rehabilitation or elderly populations.
It is precisely for this reason that there are numerous studies on this type of patients in the literature, while the production of papers on healthy patients is much more limited. In fact, although BFR training is also used on athletes during rehabilitation, it could also be very useful during athletic preparation, to limit loads and therefore limit the incidence of injuries.
The main aims of this review were to conduct a meta-analysis to examine the effects of LL-BFR training in healthy athletes, and a systematic analysis to examine study quality and reporting with a focus on safe and effective application of BFR. Thus, the objectives of this review were to: 1) compare the effects of BFR training to both low- and heavy-load training without BFR; 2) systematically review studies examining BFR training in healthy athletes; and 3) from the results of the systematic analysis, examine and provide recommendations regarding safe and effective implementation of BFR training in healthy athletes.

METHODS

This study was conducted by a research group composed by medical doctors and rehabilitation professionals from the "Sapienza" University of Rome and from "Rehabilitation & Outcome Measure Assessment" (R.O.M.A.) association. R.O.M.A. association in the last few years has dealt with several systematic reviews and the validation of many outcome measures in Italy (42-56).

Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (57), on the basis of a prospectively defined review protocol submitted to PROSPERO.

Search strategy

A literature search to identify research papers examining BFR training in healthy athletes was carried out on the following databases from inception to 1st April 2020 PubMed, Cochrane (Embase), PEDro. The title and abstract of each study were screened; exercise training studies utilizing BFR were selected. The reference list of relevant papers was also examined. The exact search terms were: “blood flow restriction” OR “occlusion” OR “kaatsu” AND “athletes” OR “sport” OR “well trained”.

Inclusion and exclusion criteria

No restrictions were applied to publication period, neither to the country in which the study was conducted. The search was limited to studies published in English. Restriction was applied on study designs. Only experimental studies were included, both Randomized Controlled Trials and Clinical Trials. Studies that include comparison between Blood Flow Restriction Training and different training (or no training) was considered. Only studies about chronic adaptments after BFR were included in this review: any acute studies, case studies, single-arm studies or those not published in a scientific peer-reviewed journal in English were excluded from meta-analysis.

Risk of Bias

Following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions (26), risk of bias was assessed using six criteria that were individually rated for each study. In this context, selection bias, performance bias, detection bias, as well as attrition and reporting bias were considered by the reviewer.

Study selection and data extraction

Titles, keywords, and abstracts identified through the databases were screened independently by two reviewers (PF and GG) and those failing to match the inclusion criteria and any duplicates were excluded. After the first screening, the primary reviewer selected the relevant studies and assessed them against the inclusion criteria. A second reviewer then cross-checked the studies. After the second screening, studies that did not fit the inclusion criteria were systematically excluded and others that appeared pertinent were identified. A final list of eligible studies was compiled, and any disagreements were resolved by a third reviewer or by consensus. From the remaining eligible papers, data were recorded relating to: 1) study design; 2) clinical population characteristics; 3) rehabilitation protocol: type, frequency, occlusion characteristics, training load and duration of BFR training; and 4) outcome measure. Data regarding the safety of BFR implementation were obtained from the systematic analysis of the studies. Data were extracted using a custom spreadsheet composed by PF.

Strategy for data synthesis

A narrative synthesis of the findings of the included studies was provided, structured around the type of intervention, BFR characteristics, type of outcome, and intervention content. A quantitative synthesis of the benefits of blood flow restriction in healthy athletes was discussed.

Meta-Analysis

Data analysis was performed by one author (PF) and reviewed by the second author (GG). The quantitative analysis was conducted by comparing outcomes. Data were extracted in the form of mean, SD, and sample size for the meta-analysis.

RESULTS

Search results

A total of 214 records were identified. Fifty duplicate records were excluded, and the remaining 164 were screened. After reading the titles, 145 studies were excluded. After the exclusion of 5 records for inappropriate research design (acute studies), 14 studies (18, 58-69) were included in the qualitative synthesis. Seven (59, 61, 63-65, 67, 69) of the 14 studies examined were included in the quantitative synthesis. **Figure 1** represents the selection process of the study. **Table I** contains information about the characteristics of included studies.

Study characteristics: clinical populations and BFR training interventions

The sample size in the studies varied from 12 (61, 66) to 62 (66) participants. The majority of the participants were men with mean ages ranging from 19.2 ± 1.8 (68) to 27 ± 3.4 years (68). One study does not report the ages of the patients (69). The subjects were athletes of different sports disciplines: football (59, 63, 64), track and field (57, 62, 69), rugby (58, 18), netball (60) basketball (61), rowing (65), futsal (66). In two studies the sport practiced was not specified (67, 68).

BFR was achieved using either pneumatic cuffs, practical cuffs, hand pumped blood pressure cuffs or elastic wraps ranging from 3 to 13 cm in width. Occlusive pressure across studies ranged from 160 to 230 mmHg. Studies either selected a pressure based on previous research, on total limb occlusive pressure, on moderate perceived pressure, or on systolic blood pressure. The duration of the BFR training intervention ranged from 3 to 8 weeks, with a frequency of 2 to 6 training sessions per week. Two studies did repeated sessions on the same day (61, 69).

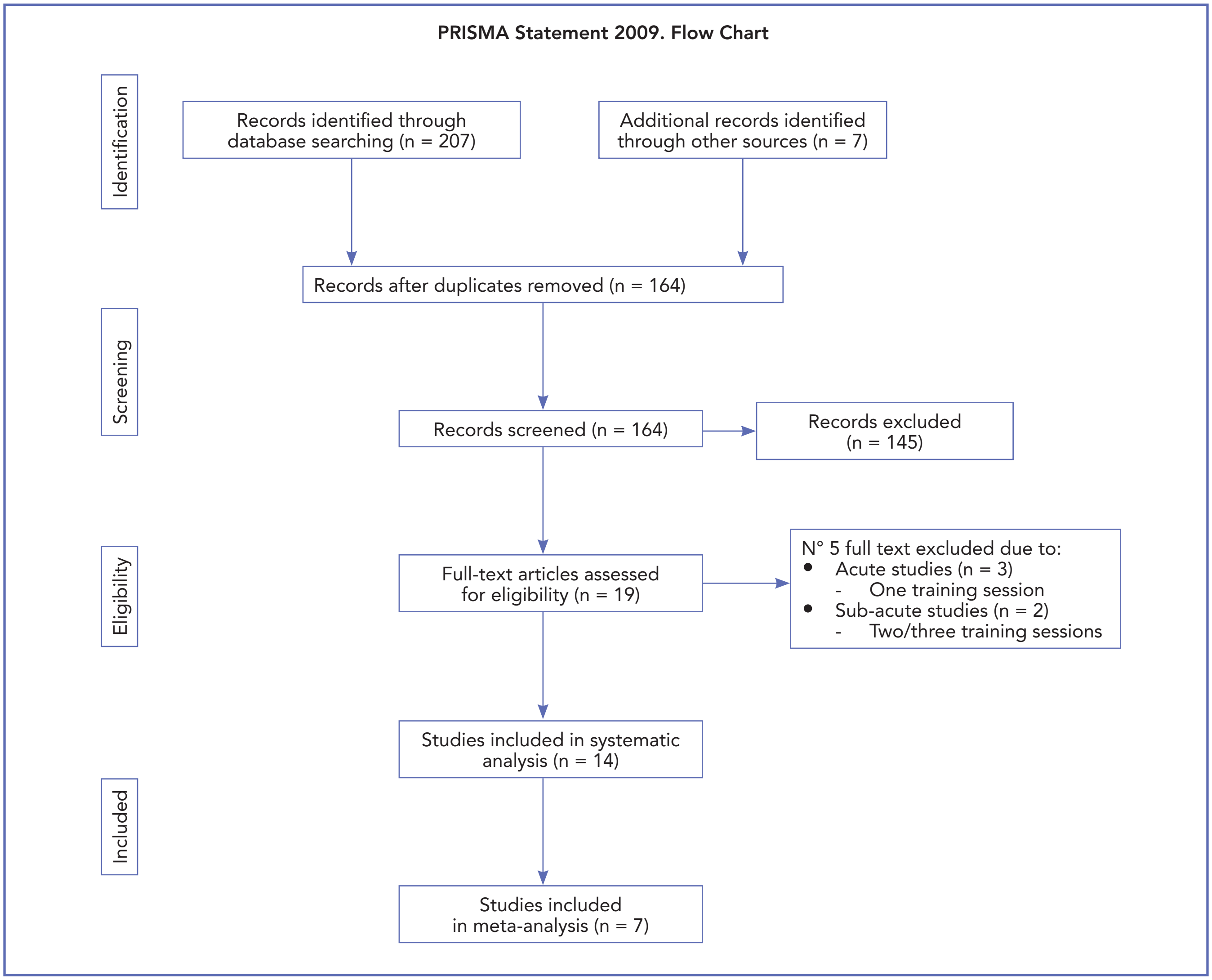

Figure 1. Flow chart of study selection process.

Outcome measures

Muscle strength was assessed by measurement of isokinetic peak torque (18, 66, 68) squat (58, 59, 63, 64, 65), bench press (58, 59, 64). Muscle size was assessed by examining muscle CSA, (60, 62, 18, 69) muscular architecture (63) and muscle thickness (57, 59, 64, 68). Cardiovascular fitness and aerobic endurance were measured by VO_2 max (60, 61, 65, 67). Studies that assessed physical function included running sprinting time (57, 60, 63, 69) running skills (67), sport related performance test (66), jumping task (60, 63, 69) and EMG values (18, 66). Studies reported hormones values, like cortisol (57, 58) testosterone (57, 58), growth hormone (57), IGF-1 (57, 66) and MSTN (66).

Risk of Bias

The main findings from the risk of bias assessment were that all the studies could not blind participants and no study included in this review specified the blinding of outcome assessment. Other main findings conceal group allocation, and sequence generation was largely unreported. From the qualitative analysis, a small number of studies were found with a high level of quality (57, 65, 68) (**figure 2**).

Meta-Analysis

There is a growing interest in the use of BFR training as a clinical MSK rehabilitation tool, and its use is becoming increas-

Table I. Characteristics of the included studies.

Reference	Subjects	Age / Gender / Body mass	Intervention group	Control group	Exercise protocol	Frequency/ duration	Cuff characteristics	Main Findings
BEHRINGER, 2016	Sprinting Runners, n=24	• 23.65 ± 2.2 years • M • 77.9 ± 7.8 kg	Exercise protocol + BFR n=12	Exercise protocol n=12	6 consecutive 100m sprints at intensity of 60/70% of their predetermined best sprinting performance	2 times a week, for 6 week	Elastic knee wraps, 200 x 13 cm, with moderate perceived pressure (7 on a scale of 0 to 10)	Significant ($p<0.05$ pre) improvements were observed in IG: ↓ 100m time (s), -0.38 (0.24, -0.51) ↑ muscle thickness of rectus femoris (mm), +1.5 (0.8, 2.1) ↑ muscle thickness of biceps femoris (mm), + 1.8 (1.2, 2.4) ↑ RFD Leg Press (kN*s-1), 6.0, (1.7, 10,2) ↔ Growth hormone, testosterone, cortisol, insulin-like growth factor1 • The muscle damage marker h-FABP increased significantly more in the CG than in the IG
COOK, 2014	Rugby Players n=20	• 21.5 ± 1.4 years • M • 95.6 ± 10.4 kg	Exercise protocol + BFR n=10	Exercise protocol n=10	3 exercises (leg squat, bench press, weighted pull-up) at 70% of their 1RM. 5 sets of 5 repetition - 90 seconds rest between sets, 3 minutes between exercises.	3 times a week, for 3 weeks	Occlusion Cuff width 10.5 cm inflated to 180 mmHg	Greater improvements were observed (occlusion training vs control) in: ↑ bench press (kg) 5.4 ± 2.6 vs 3.3 ± 1.4 ↑ squat (kg) 7.8 ± 2.1 vs 4.3 ± 1.4 ↑ maximum sprint time (s) –0.03 ± 0.03 vs –0.01 ± 0.02 ↑ leg power (W) 168 ± 105 vs 68 ± 50 • Greater exercise-induced salivary testosterone (ES 0.84–0.61) and cortisol responses (ES 0.65–0.20) were observed in IG compared with CG; however, the acute cortisol increases were attenuated across the training block
LUEBBERS, 2014	Collegiate American football n=62	• 20.3 ± 1.1 years • M • 99.1 ± 19.7 kg	High intensity training program + supplemental 20% lifting + BFR n=17	High intensity training program + supplemental 20% lifting n=14 | High intensity training program n=15 | Modified training program + supplemental 20% lifting + BFR n=16	Traditional American football training + Supplemental squat and bench press at 20% 1RM. 1 set of 30 rep + 3 sets of 20 rep	4 times a week, for 7 weeks	Elastic knee wraps, 167.6 x 7.36 cm, graduated every 1,3 cm perpendicular to the edge with a silver permanent marker. Wraps were pulled to a 7.6 cm overlap as measured by the silver markings.	↑ 1RM squat +12.89% - Significant interaction, F (3.57) = 6.460, p = 0.001, η^2 = 0.254 • Results of Fisher LSD post hoc tests revealed that the IG group experienced greater gains in 1RM squat performance than did the M/S/R group (p , 0.000), the H/S group (p = 0.025), and the H group (p = 0.009). ↑ Bench press +7.06% • Although the t-test on 1RM bench revealed that there was a significant increase across groups (t(1,61) = 6.713, p , 0.000), the ANOVA did not detect differences between the groups (F(3,58) = 1.687,p . 0.180). ↑ Arm and Thigh girth - the ANOVA did not detect differences between groups ↔ Chest girth

Reference	Subjects	Age / Gender / Body mass	Intervention group	Control group	Exercise protocol	Frequency/ duration	Cuff characteristics	Main Findings
MANIMMANAKORN, 2013	Netball players n=30	• 20.2 ± 3.3 years • F • 65.2 ± 6.5 kg	Exercise protocol + BFR n=10	Exercise protocol n=10 | Exercise protocol + intermittent hypoxic training n=10	Three sets of knee extension followed by three sets of knee flexions to failure (total of 6 sets) with a 30 s rest between sets and a 2 min rest between exercises using an isotonic leg extension and flexion machine.	3 times a week, for 5 weeks	Pneumatic cuff, 5 cm width, 160 to 230 mmHg	Relative to IG: ↑ MVC3 (11.0 ± 11.9%) ↑ MVC30 (10.2 ± 9.0%) ↑ Reps201RM (28.9 ± 23.7%) ↑ CSA (6.6 ± 4.5%) ↑ Vertical Jump (4.8 ± 10.0%) ↑ 20-MST (11.7 ± 7.4%) ↑ MAS (3.3 ± 2.0%) ↑ V02 max (5.1 ± 3.9%) ↓ 5m Sprint (-16.3 ± 14.4%) ↓ 10m Sprint (-3.3 ± 5.2%) ↓ 505 Agility (-9.0 ± 6.7%)
PARK, 2010	Collegiate Basketball players n=12	• 20.45 ± 1.25 years • M • 88.15 ± 6.65 kg	Exercise protocol + BFR n=7	Exercise protocol n=5	5 sets of 3-min walking (4 km/h at 5% grade) on a motorized treadmill and a 1-min rest between walk-sets (19 min of total time). The walking speed was increased up to 6 km/h in the OCC-walk group while it remained constant throughout the training period in the NOR-walk group	2 times a DAY, 6 days a week, 2 weeks	Pneumatic cuff, 11 cm width, 160 to 220 mmHg	↑ Vo2max (+11.6%: P=0.005) ↑ VE max (+10.6%: P=0.003) ↑ Anaerobic capacity (Wingate test) (+2.5%: P=0.022) ↔ No difference in muscular strength
SAKURABA, 2009	Track and field athletes n=21	• 19.9 ± 0.6 years • M • 65.9 ± 0.7 kg	High speed exercise protocol + BFR n=6 | Low speed exercise protocol + BFR n=4	High speed exercise protocol n=6 | Low speed exercise protocol n=5	3 sets of repeated isokinetic extension and flexion of the knee joint, repeated 10 times, with a 60-s rest between sets. Load was 90°/s (Low speed) to 300°/s (High speed)	2 times a week, for 4 weeks	Cuff width not reported inflated to 200 mmHg	In a comparison of groups HS-IG and HS-CG, there were significant increases with an angular velocity of 300°/s for CC and 60°/s for EC ($P < 0.05$) ↑ Knee extensor muscular strength ↔ CSA of femoral muscle, determined by RMN
SCOTT, 2016	Semi professional football players n=18	• 19.8 ± 1.5 years • M • 80.8 ± 8.2 kg	Exercise protocol + BFR n=10	Exercise protocol n=8	Normal resistance, conditioning and football training session + low load squatting exercise	3 times a week, for 5 weeks	Elastic powerlifting knee wraps, 7.5 cm x 250 cm	↔ Muscular architecture ↔ Performance in sprinting and jumping tasks ↑ Squat 3RM (+12.3%; P=0.007) ↑ Squat endurance (+21.2%; P=0.007) • No between-group differences, IG - CG

Reference	Subjects	Age / Gender / Body mass	Intervention group	Control group	Exercise protocol	Frequency/ duration	Cuff characteristics	Main Findings
TAKARADA, 2002	Elite rugby players n=17	• 25.73 ± 0.76 years • M • 91.93 ± 6.6 kg	Exercise protocol + BFR n=6	Exercise protocol n=6 | Untrained control n=5	4 sets of repeated bilateral isokinetic extension of the knee joint; mean repetition in each set was 16,3 times, with a 30-s rest between sets. Load was 50% of 1RM	2 times a week, for 8 weeks	Elastic belt, 80 cm x 33 mm width, inflated to (mean) 196 mmHg	↑ Isokinetic knee extension torque (+14.3 ± 2.0%; P<0.05) in IG ↑ CSA of extensor muscles (+12.3 ± 0.8%) in IG ↓ Fatigue indices in IG: [work] from 63.7 (2.3) to 58.7 (2.3)% (P=0.002) and [peak torque] from 61.3 (2.1) to 53.7 (4.0)% (P=0.002) ↔ iEMG signals, IG and CG
YAMANAKA, 2012	NCAA Division I A football athletes n=32	• 19.2 ± 1.8 years • M • 89.6 ± 2.7 kg	Exercise protocol + BFR n=16	Exercise protocol n=16	In addition to regular off-season football strength training program, 4 sets of bench press and squat. 30-20-20-20 repetition scheme (45 s inter-set rest, 20% 1RM)	3 times a week, for 4 weeks	Elastic bands (5 cm x 55 cm for upper body, 5 cm x 90 cm for lower body)	↑ 1RM bench press (+7%; P<0.05) in IG ↑ 1RM squat (+8%; P<0.05) in IG ↑ Girth of upper chest (+3%; P<0.05) in IG ↑ Girth of lower chest (+3%; P<0.05) in IG ↑ Girth of left arm (+2.27%; P<0.05) in IG
HELD, 2019	Elite Rowers n=31	• 21.8 ± 3.45 years • M=23/F=8 • 73.05 ± 11.5 kg	Training + BFR n=16	Training n=15	rowing (low, moderate and high intensity), cross (running and cycling) and strength training - at low intensities (<2 mmol/L)	3 times a week, for 5 weeks	Elastic knee wraps, 200 x 13 cm, with moderate perceived pressure (7 on a scale of 0 to 10)	↑ VO˙ 2max (+9.1 ± 6.2%) in IG ↔ SQ1RM
AMANI-SHALAMZARI, 2019	Futsal players n=12	• 23 ± 2 years • M • 67.5 ± 6.8 kg	Exercise protocol + BFR n=6	Exercise protocol n6	3-a-side game training	2/3 times a week, for 3 weeks (total 10 sessions)	Pneumatic cuffs (13 × 124 cm), inflated from 110% of leg systolic blood pressure, increased by 10% after every two completed sessions	↑ Peak torque for knee extension (30% ± 8.0 in IG vs 14.9 ± 7.5% in CG) ↑ Peak torque for knee flexion (23.8% ± 8.4 in IG vs 8.1 ± 5.7% in CG) ↑ iEMG m. vastus lateralis, m. vastus medialis, m. rectus femoris (m. rectus femoris significant difference between groups, in favor of IG) ↓ Performance Time for FSPT test (-11% in IG vs -6% in CG) ↔ IGF-1 levels ↓ Resting levels of MSTN, significantly in IG ↑ Resting post-training IGF-1/ MSTN ratio

Reference	Subjects	Age / Gender / Body mass	Intervention group	Control group	Exercise protocol	Frequency/ duration	Cuff characteristics	Main Findings
PATON, 2017	Recreational Athletes n=16	• 25 ± 7 years • M=10/F=6 • 75 ± 14 kg	Running Training + BFR n=8	Running Training n=8	Running at 80% of PRV on a treadmill. Repeated bouts of 30-s efforts interspersed with 30-s of passive rest, from 2 sets of 5 rep to 3 sets of 8 rep. 150s rest interset.	2 times a week, for 4 weeks	Elastic knee wraps, width 7.5 cm, with moderate perceived pressure (7 on a scale of 0 to 10)	↑ VO˙ 2max (+6.3 ± 3.5%) in IG vs (+4.0 ± 3.3%) in CG - (ES=0.18 in favor of IG) ↑ TTE (+27 ± 9%) in IG vs (+17 ± 6%) in CG - (ES=0.31 in favor of IG) ↑ Running economy only in IG (ES=0.4 in favor of IG) ↑ PRV and Incremental time, both in IG and CG, (ES=0.3 in favor of IG)
BOWMAN, 2019	Recreational Athletes n=26	• 27 ± 3.4 years • M=10/F=16 • not reported	Exercise protocol + BFR one limb n=16	Exercise protocol n=10 | Exercise protocol + BFR limb NON OCCLUDED n=16	Straight-leg raise hip flexion, side-lying hip abduction, long-arc quadriceps extension, standing hamstring curl. For each exercise, 30-15-15-15 repetition scheme (30 s inter-set rest, 30% 1RM)	2 times a week, for 6 weeks	Pneumatic tourniquet, 10.16 cm (4 inches) width, inflated to 80% of arterial occlusion	↑ Peak torque for knee extension (11% in IG vs 3% in CG) - ($P<0.04$) ↑ Total work (15% in IG vs 6% in CG) - ($P<0.04$) ↑ Average power (12% in IG vs 4% in CG) - ($P<0.04$) ↑ Thigh circumference (3.5% in IG vs 0.8% in CG) - ($P<0.01$) ↑ Leg circumference (2.8% in IG vs 0.4% in CG) - ($P<0.01$) ↑ Thigh circumference (2.3% in NON-bfr IG vs 0.8% in CG) - ($P<0.05$) ↑ Peak torque for knee extension (8% in NON-bfr IG vs 3% in CG) - ($P<0.05$)
ABE, 2005	Track and field college athletes n=16	• not reported • M • 66.85 ± 4.4 kg	Regular Training + Resistive exercise + BFR n=9	Regular Training n=6	Squat and leg curl. For each exercise, 3 set of 15 reps, 20%1RM. 30s rest interset.	2 times a DAY, for 8 days	Elastic belt, width Not reported, with pneumatic bag inflated 160 to 230 mmHg	↑ Muscle-bone estimated CSA (+4.5%) in IG vs (-1%) in CG ↑ Quadriceps MTH (+5.9% in IG, no change in CG) - $p<0.01$ ↑ Hamstrings MTH (+4.5% in IG, no change in CG) - $p<0.01$ ↑ Leg press (9.6% in IG vs 4.8% in CG) - $p<0.01$) ↓30-m dash Times, specially in 0-10 phase (only in IG, no change in CG) - $p<0.01$ ↔ No change in jump performance in both groups

RFD, rate of force development; CG, control group; IG, intervention group; MCV3, 3-s maximal voluntary contraction; MCV30, 30-s maximal voluntary contraction; Reps201RM, number of repetitions at 20% 1RM; CSA, cross-sectional area; 20-MST, maximal multistage 20-m shuttle run test; MAS, maximal attained speed; V-O_2max Maximum oxygen uptake; VE max, maximal minute ventilation; HS-IG, high speed intervention group; HS-CG, high speed control group; CC, concentric contraction; EC, eccentric contraction; 3RM, 3-repetition maximum; iEMG, integrated electromyography; SQ1RM, one-repetition maximum squat test; FSPT, Futsal Special Performance Test; IGF-1, insulin growth factor-1; MSTN, myostatin; TTE, time to exhaustion; PRV, peak running velocity, MTH, mid-thigh muscle thickness.

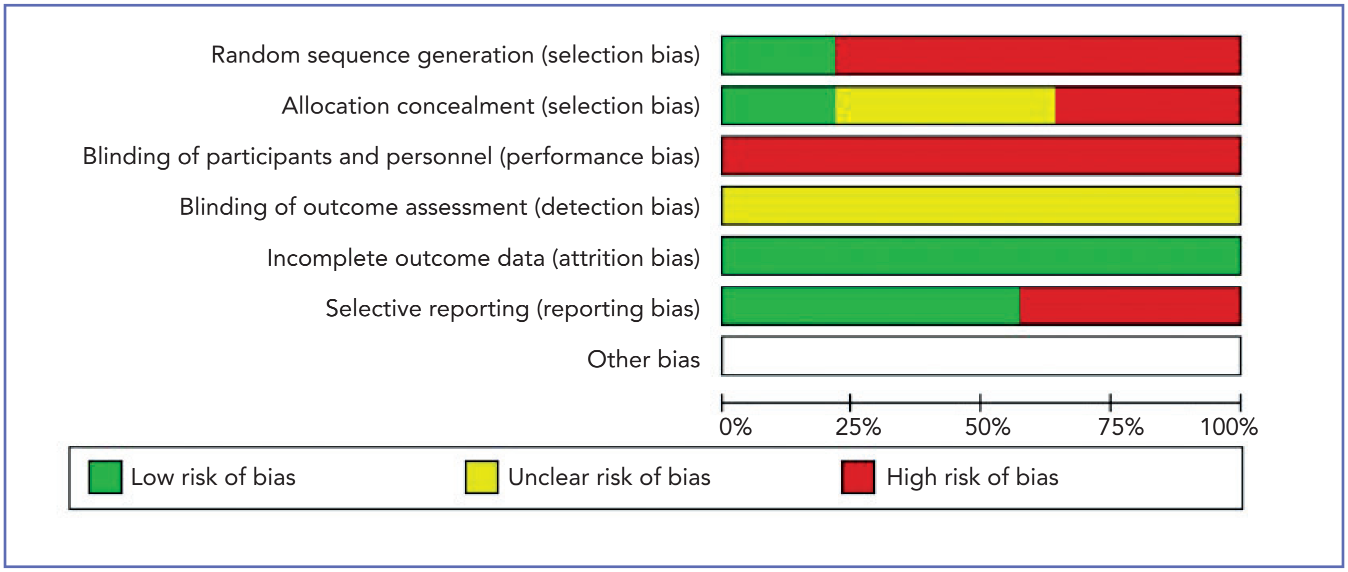

Figure 2. Risk of bias.

ingly widespread, even for athletic preparation. However, the effectiveness of this novel training modality in healthy athletes has not been examined. Therefore, this review has provided insight into its effectiveness in healthy athletes.
The quantitative analysis was carried out by comparing outcomes and follow-ups. This pool was based on comparable outcomes, and comparable times of follow-up has allowed consideration of seven studies in the meta-analysis, with six comparable outcomes:
Those studies are as follows:
1. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 1: VO_2 max (ml/min/kg), follow-up 2-6 weeks. The studies of Park *et al.* (2010), Held *et al.* (2019) and Paton *et al.* (2017) (61,65,67) were considered. At baseline, there are no differences between the groups, which are homogeneous (P = 0.86). Mean difference = 0.33, 95% Confidence Interval (CI) = - 2.87, 3.52. Meta-analysis revealed statistically significant results (P = 0.0002) in favor of the experimental group compared to the control group (mean difference = 5.33, 95% Confidence Interval (CI) = 2.54, 8.11) (**figure 3**).
2. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 2: Bench press (kg) follow-up 4-7 weeks. The studies of Yamanaka *et al.* (2012), and Luebbers *et al.* (2014) (64, 59) were considered. At baseline, there are differences between the groups, which are heterogenous (P = 0.007). Mean difference = 3.87, 95% Confidence Interval (CI) = - 4.76, 12.49. Meta-analysis revealed results statistically not significant (P = 0.10) in favor of the experimental group compared to the control group (mean difference = 7.75, 95% Confidence Interval (CI) = - 1.46, 16.96) (**figure 4**).
3. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 3: Squat (kg) follow-up 4-7 weeks. The studies of Yamanaka *et al.* (2012), and Luebbers *et al.* (2014) (64,59) were considered. At baseline, there are differences between the groups, which are heterogenous (P = 0.005). Mean difference = - 5.96, 95% Confidence Interval (CI) = - 17.36, 5.43. Meta-analysis revealed results statistically not significant (P = 0.06) in favor of the experimental group compared to the control group (mean difference = 11.46, 95% Confidence Interval (CI) = - 0.66, 23.58). Heterogeneity change, (P = 0.54), which represents moderate heterogeneity in the results (**figure 5**).
4. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 4: Thigh Girth (cm) follow-up 4-7 weeks. The studies of Yamanaka *et al.* (2012), and Luebbers *et al.* (2014) (64, 59) were considered. At baseline, P = 0.25 groups represented moderate heterogeneity in the results. Mean difference = - 0.07, 95% Confidence Interval (CI) = - 2.38, 2.25. Meta-analysis revealed results statistically not significant (P = 0.58) in favor of the experimental group compared to the control group (mean difference = 0.66, 95% Confidence Interval (CI) = - 1.67, 3.00). Heterogeneity change, (P = 0.11), which represents higher heterogeneity in the results (**figure 6**).
5. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 5: Chest Girth (cm) follow-up 4-7 weeks. The studies of Yamanaka *et al.* (2012), and Luebbers *et al.* (2014) (64, 59) were considered. At baseline,

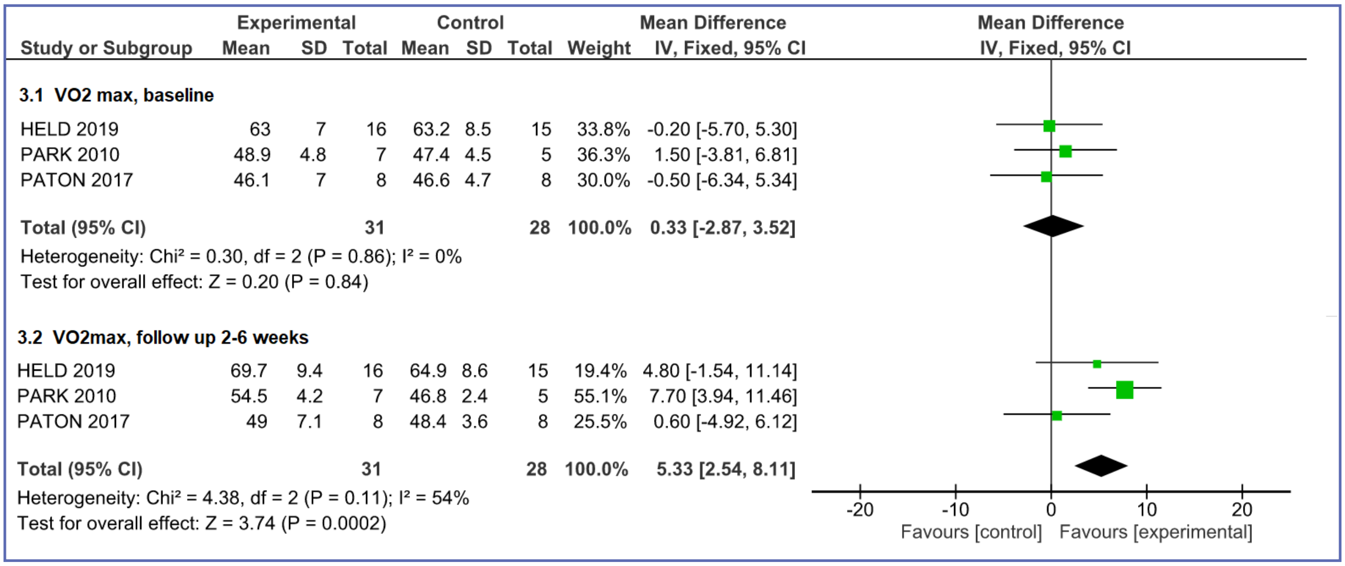

Figure 3. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 1: VO_2 max.

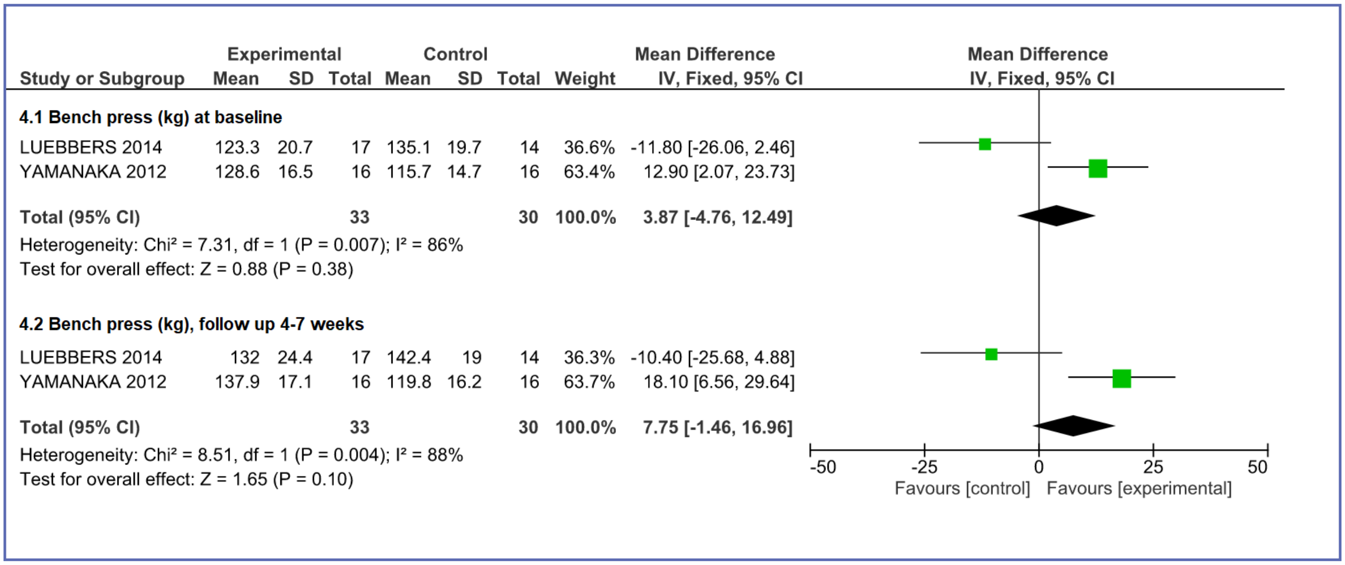

Figure 4. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 2: Bench press (kg).

P = 0.32 groups represented moderate heterogeneity in the results. Mean difference = - 0.78, 95% Confidence Interval (CI) = - 4.09, 2.53. Meta-analysis revealed results statistically not significant (P = 0.89) in favor of the experimental group compared to the control group (mean difference = 0.22, 95% Confidence Interval (CI) = - 2.83, 3.27). Heterogeneity change, (P = 0.15), which represents higher heterogeneity in the results (**figure 7**).

6. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 6: 0-10 m Dash time (sec) follow-up 15-16 sessions. The studies of Scott *et al.* (2016), and Abe *et al.* (2005) (63, 69) were considered. At baseline, mean difference was = 0.02, 95% Confidence Interval (CI) = - 0.03, 0.08. Meta-analysis revealed results statistically not significant (P = 0.54) in favor of the experimental group compared to the control group (mean

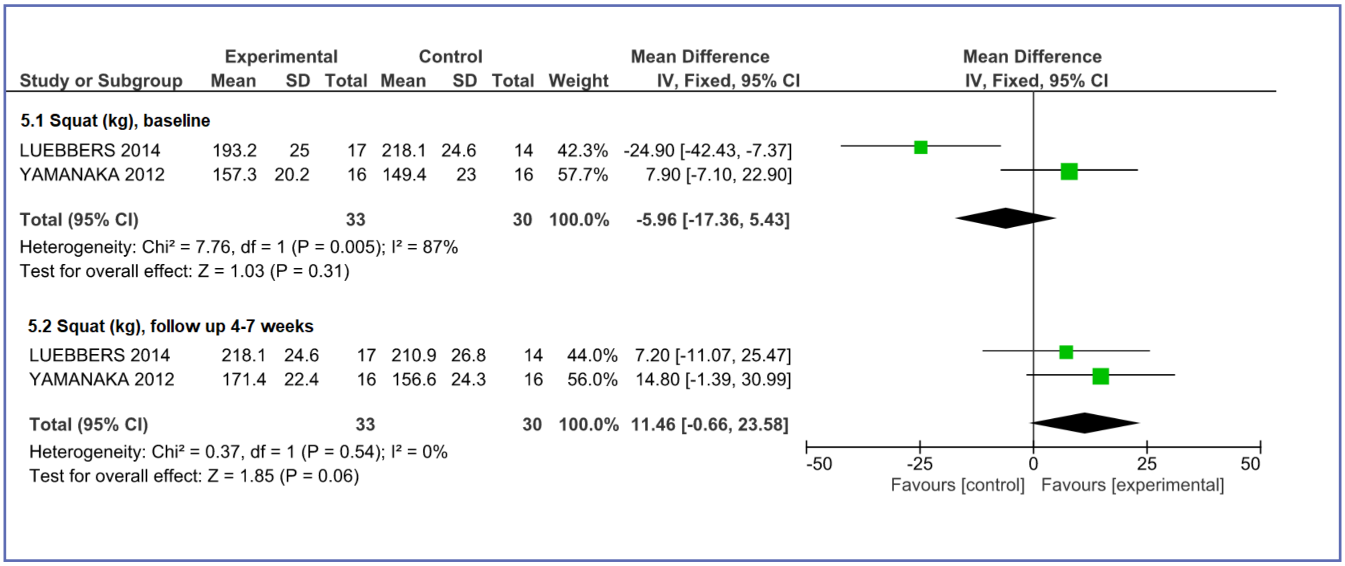

Figure 5. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 3: Squat (kg).

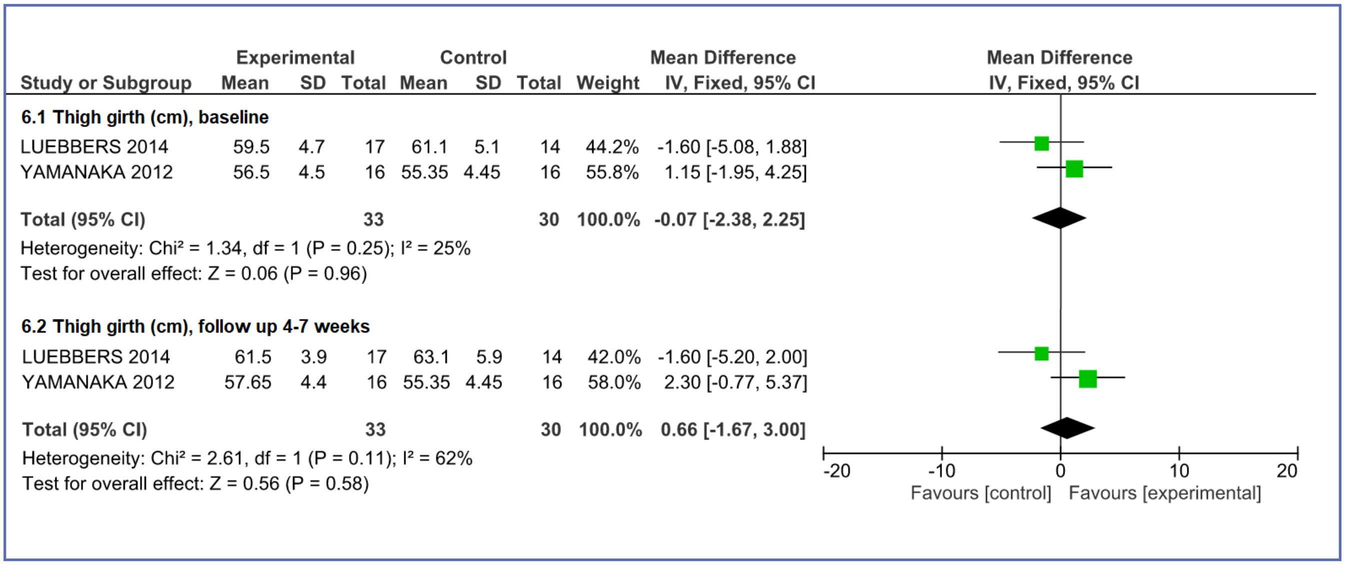

Figure 6. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 4: Thigh Girth (cm).

difference = 0.01, 95% Confidence Interval (CI) = - 0.03, 0.06 (**figure 8**).

DISCUSSION

The meta-analysis has pointed out that Blood Flow Restriction Training could be a valid option for improve physical performances in healthy athletes.

The quantitative analysis in the studies of Park *et al.* (2010), Held *et al.* (2019) and Paton *et al.* (2017) (61, 65, 67) underlines statistically significant results (p = 0.002) concerning VO_2max, with a large increase in favor of BFR group.

Several studies (61, 67, 70-75) as discussed in a recent review (76) directly looked at the impact of BFR combined with aerobic exercise on aerobic capacity and performance, reporting that BFR during aerobic exercise at light inten-

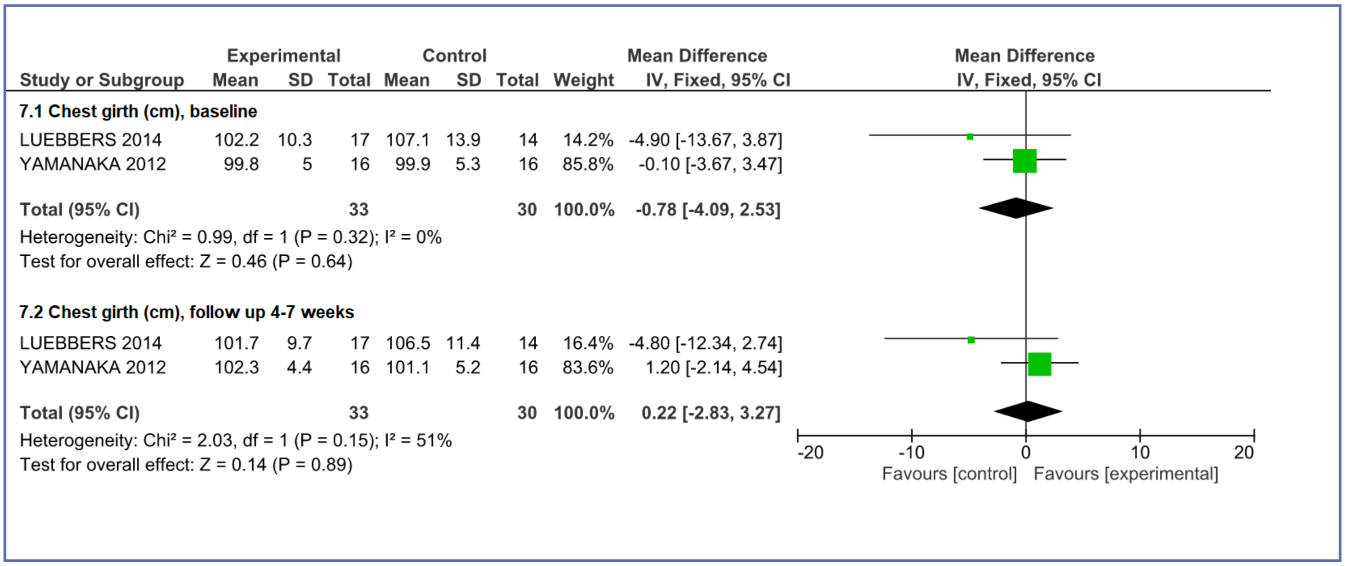

Figure 7. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 5: Chest Girth (cm).

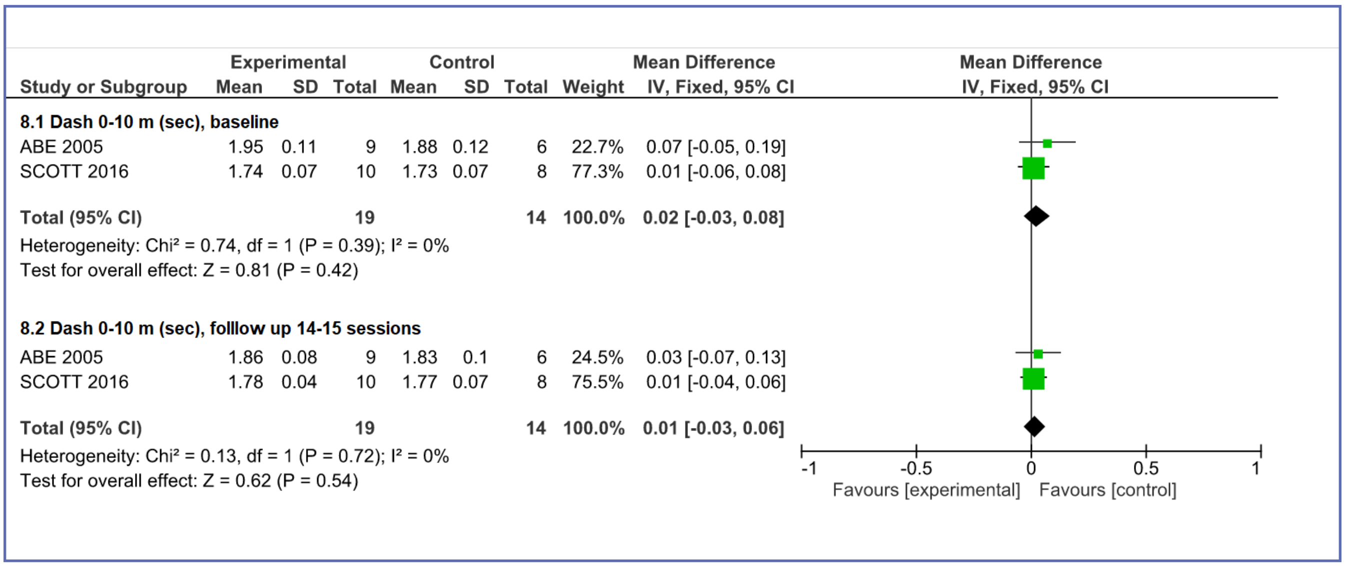

Figure 8. Comparison of exercise protocol + BFR *vs.* exercise protocol concerning outcome 6: Dash 0-10 m (sec).

sities caused improvements in aerobic fitness and aerobic performance in young adults when using occlusion pressures of 130 mmHg or greater. Proposed mechanisms for the $VO^{\cdot}_2$ max adaptations of BFR amplification, are the following: BFR can increase the central cardiovascular response during exercise (77) by elevating heartrates, systolic blood pressure and diastolic blood pressure compared to the same exercise under non-occluded conditions (78-80).

One study reported a decline in both metabolite clearance and oxygen delivery during BFR application (81).

In recent times, Christiansen *et al.* (82) showed increases in muscle ancillary protein, peroxisome proliferator-activated receptor-γ co-activator 1α (PGC-1α mRNA) and phospholemman isoforms (FXYD1) during BFR exercise, which was related to increased oxidative stress and fiber type-dependent AMPK signaling.

Generalizing, it's possible argue that the described acute responses of BFR might have led to a greater training stimulus (compared to none BFR training), which could induce corresponding $\dot{VO}_2$ max improvements. However, this remains speculative. Our study indicates that that the application of BFR induces large increases of $\dot{VO}_2$ max even in highly trained athletes, and this makes the results even more noteworthy.

The qualitative analysis of the RCTs included in this systematic review provides interesting results regarding strength improving. The quantitative analysis shows significant results, even if not statistically relevant (P = 0.06) concerning muscle strength evaluated with Squat (kg) in the studies of Yamanaka *et al*. (2012), and Luebbers *et al*. (2014) (64, 59). Interestingly, even if at baseline the mean difference was - 5.96 in favor of CG, after intervention became + 11.46 in favor of IG, with a significant improvement in squat performances.

The results are similar on the bench press, although not statistically significant (P = 0,10) as shown in meta-analysis. In this context, reviews (12) and meta-analyses (83, 84) showed that low load training with BFR application induced superior strength and hypertrophy adaptations than low load training without BFR. BFR methods seemed to generate similar hypertrophy adaptations when compared to high load resistance training, but lower strength adaptations (84).

Endurance and strength capacities are recommended to be trained separately (85) as interference effects between strength and endurance stimuli can hamper simultaneous adaptational processes of both components (86). Since the subjects' training was mixed, both strength and endurance, we can say that the results at strength level are even more interesting.

Concerning girth's studies, analyzed in the studies of Yamanaka *et al*. (2012), and Luebbers *et al*. (2014) (78, 73), neither those on the thigh nor those on the chest were statistically significant, although they both showed improvements. From baseline, mean difference (cm) was + 0.73 for thigh and + 1.00 for chest.

Comparison concerning 0-10 dash time analyzed in the studies of Scott *et al*. (2016), and Abe *et al*. (2005) (63, 68) didn't reveal results statistically relevant, and no change between IG and CG. We would point out, however, that in one of the two studies (Abe) (69) only the IG was subjected to additional training, with an exposure to exercise not equal between groups.

Thus, BFR provides a feasible, promising, and beneficial complementary training stimulus to traditional training when used in a controlled environment supervised by trained and experienced personnel.

Study Limits

The present meta-analysis has some limitations.

There are some limitations in the present meta-analysis that should be mentioned. Although the field of BFR training is a frequently discussed topic in scientific research, the number of studies investigating the effects of BFR in healthy athletes is still sparse. For this reason, one limits of this study concern the small number of patients in the trials and the small number of RCTs in the literature. The subjects practiced very different sports, which leads to very different training modalities and varied physiological responses. A 100-meter runner will not have the same adaptive response as a rower or a cyclist. Several outcome's measures were taken with various methods and therefore could not be directly compared with one another. Anthropometric measures of muscle size pose obvious limitations because they are not reflective of composition: they only make up a portion of the district examined. Anthropometric measures are not specific: they may also vary due to other factors, regardless of muscle mass development (*e.g.,* fat accumulation). The lack of a standardized protocol also created other difficulties, as some studies implemented sets to volitional fatigue, while others used a more common protocol consisting of 1 set of 30 repetitions followed by 3 sets of 15. It should be however taken into account that the training and BFR modalities (2-12 sessions per week; 2-8 weeks duration of intervention; 160-230 mmHg BFR cuff pressure, width of the cuff 3.3-13 cm) have varied greatly among previously conducted studies. Importantly, occlusion pressure is heavily affected by cuff width, as wider cuffs require lower absolute pressures to similarly reduce blood flow as compared with narrow ones. Those variabilities underpin the importance of future studies to standardize interventions (duration of BFR intervention, accumulated BFR duration per week, type of training, cuff's standards, and other aspects). Uniformity of outcome measures and better quality of studies would also be desirable.

CONCLUSIONS

The present systematic review and meta-analysis provides novel insights into the effect of BFR training compared with traditional training modalities in healthy athletes.

Although the research on this topic is limited, our results indicate that the application of BFR positively influences muscular adaptations compared with exercise under normal blood-flow conditions, in terms of higher strength increase and muscles adaptations. However, the comparison between BFR-training and Non-BFR training requires further research utilizing more standardized protocols for appropriate comparison. An important finding from this review illustrated that BFR can increase VO_2 max, improving aerobic capacity. It should be considered that since the subjects in the studies were sportsmen, and therefore already trained, these results appear even more interesting. Additionally, we want to draw attention to the lack of high-quality studies concerning the effects of BFR in healthy athletes. Future research should adopt an individualized and progressive approach to facilitate the effectiveness and safety of BFR training, and standardized protocols in order to facilitate the comparison. In conclusion, this first systematic review and meta-analysis on healthy athletes, suggests that training with BFR can be a good strategy for improving sports performance, without the loads of HL training. The study was conducted according to the journal's guidelines (88).

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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