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Does blood flow restriction training increase the diameter of forearm vessels in chronic kidney disease patients? A randomized clinical trial

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Abstract

Introduction: Blood flow restriction training can be used as an alternative to conventional exercise in chronic kidney disease patients with indication of arteriovenous fistula.

Objective: Evaluating the efficacy of blood flow restriction training in the diameter and distensibility change of the cephalic vein and the diameter and flow of the radial artery, muscle strength and forearm circumference in chronic kidney disease patients with arteriovenous fistula pre-creation.

Methods: A blind randomized clinical trial consisting of 26 chronic kidney disease patients allocated into a blood flow restriction training group (blood flow restriction; $n = 12$) and a group without blood flow restriction training (control group; $n = 14$). Blood flow restriction was performed at 50% of systolic blood pressure and using 40% of handgrip strength as load for the isometric exercises in both groups.

Results: An increase in the diameter of the cephalic vein in the 2 cm ($p = 0.008$) and 10 cm segments ($p = 0.001$) was observed in the control group. The diameter of the radial artery increased in all segments in the blood flow restriction group (2, 10 and 20 cm; $p = 0.005$, $p = 0.021$ and $p = 0.018$, respectively) and in the 10 and 20 cm segments ($p = 0.017$ and $p = 0.026$) in the control group. Handgrip strength only increased in the control group ($p = 0.003$).

Conclusion: Physical training associated with blood flow restriction increased cephalic vein diameters in both groups and was effective in increasing the diameter of the radial artery; however, it did not demonstrate superiority over the exercise group protocol without blood flow restriction.

Keywords

Arteriovenous fistula, chronic renal insufficiency, isometric exercise, vascular endothelium

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Introduction

Arteriovenous fistula (AVF) failure to mature remains a barrier to successful AVF use for dialysis treatment.[1–5] There is evidence that performing isometric forearm exercises pre- and post surgery can improve vessel quality and potentially aid AVF maturation.[6] In studies unrelated to dialysis access, blood flow restriction (BFR) has been shown to increase muscle mass and strength and has allowed use of lower intensity training regimes.[7]

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BFR in association with physical training is used to stimulate a rapid increase of specific metabolic enzymes for muscle mass and strength.[8] In addition to low exercise intensities, BFR represents an alternative training method for individuals who are intolerant to high-intensity protocols.[9]

To date, there have been no studies using BFR associated with physical exercise in chronic kidney disease (CKD) patients with AVF creation indication in the forearm.[9–13] Forearm exercise training is a therapeutic possibility that aims to reduce the high incidence of AVF maturation failure in the first year of its creation. Its use in association with BFR can promote the necessary vessel dilatation before its creation, thereby facilitating the maturation process, preventing complications and prolonging its use.[14] Thus, trying to establish an exercise program that increases the vessel diameter in patients to undergo AVF creation may provide better evidence for successful training in clinical practice.

Therefore, this study's objective was to evaluate the efficacy of BFR training on vessel diameter and flow, muscular strength and forearm circumference in patients with CKD before AVF creation.

Methods

Study design

This is a randomized controlled double-blind trial with allocation secrecy, developed from March 2016 to January 2017. The protocol was approved by the Research Ethics Committee of the institution (protocol number 1349.017) and registered in the *Clinical Trials* under number NCT02619968. This study followed the norms of the CONSORT statement.[15]

Sample

Patients with stage 4 and 5 CKD diagnosis with an indication for AVF creation, 18 years of age or older, of both genders and referred by the *Hospital das Clínicas* of the Universidade Federal de Pernambuco in conservative or dialytic treatment participated in the study. Patients were excluded if they presented cognitive deficit; had prior history of AVF creation in the upper limbs or other vascular surgical procedures in the upper limbs or in close regions; those who performed any type of manual work with heavy loads; those with untreated orthopaedic injuries in the cervical region, shoulder, elbow, wrist, and/or hand; and those who have signs of thrombophlebitis and/or hypoplasia/agenesis of the upper limbs.

The sample size was estimated based on the study by Uy et al.[6] according to the outcomes: radial artery diameter, radial artery average speed and flow peak, and cephalic vein diameter. Mean and standard deviation of the variables were used, and the cephalic vein diameter variable was considered for determining the sample as it presented the largest sample size represented by 18 patients: 9 for the experimental group and 9 for the control group (CG). However, considering a loss of 20% during the study, this sample consisted of 26 patients. Sample calculation considered a power ($1-\beta$) of 95%, an α of 5% and an effect size of 1.8667 and was performed in the G*Power 3.1.9.2 statistical program.[16]

Randomization and allocation secrecy

Randomization and allocation secrecy was performed by researchers not involved in recruitment, intervention or data collection, using a random sequence generated in blocks by the site http://randomization.com, and selected in a consecutive and random manner. Patient data were stored in black and opaque envelopes, sealed and sequentially numbered.

Outcomes. The primary outcome was increased cephalic vein diameter (mm) of at least 0.22 mm after local physical BFR training.[10] Secondary outcomes were increased cephalic vein distensibility after tourniquet placement (mm); increased radial artery diameter; increased systolic flow peak (cm/s) and mean velocity (cm/s) in the upper limbs; increased forearm circumference (cm) and increased handgrip strength (kgf).

Procedure

Patients were screened at the nephrology outpatient clinic.

Vessel morphology

Vessel morphology was performed by ultrasonography (SonoaAce R3; Samsung Medison, South Korea), using a 10 MHz multifrequential linear transducer on three different forearm sites (2, 10 and 20 cm) using the styloid radium process as anatomical reference.[10,17,18]

Handgrip strength

A manual dynamometer was used (Dynamometer Smedley; Saehan, South Korea) to evaluate handgrip strength on the one-repetition maximum (1-RM) test. Three tests with a rest interval of 2 min between them were performed and the highest value was considered.[19]

Forearm circumference

Forearm circumference was measured by perimetry using a retractable measuring tape (Sun Special, Brazil), distally placed 2 cm from the ulnar fossa.[19] Three measurements were performed and the highest value was recorded.

Intervention protocol

The patients were distributed into the experimental group (exercise with restriction BFR) and CG after randomization. The protocol was developed two times a week every other day in an outpatient setting, supervised by the same instructor and unsupervised modality (at home, three times a week on alternate days to outpatient trainings) for 8 weeks for both groups.

The BFR group performed the exercise with partial blood flow occlusion using a tensiometer positioned on the arm. The CG performed the same exercises with the tensiometer, although without any pressure (deflated); 2-min intervals were performed between each exercise modality.

Protocol for BR

The protocol for BFR was determined by inflating a tensiometer on the non-dominant upper arm with a stethoscope (3M™ Littmann® Classic II standard error (SE), USA) placed on the medial region of the elbow fold to verify the absence of the arterial pulse. BFR artery occlusion pressure was 50% of the systolic blood pressure obtained during the training and was maintained during all three exercise modalities.[20]

Exercise program

Tennis ball. Six series of 10 tennis ball squeezes were initially performed with a 1-min rest interval between sets.[19] Five more squeezes were added each week. This was the only exercise done at home following the same protocol.

Dumbbells. Weightlifting was performed by elbow flexion (3 sets of 10 movements). Lifting was performed using a 1 kg rubberized weight (Polimet, Brazil) for the first two weeks, followed by 2 kg weights for the last two weeks of the first month, and then 3 kg weights for the last four weeks, according to the modified protocol used by Salimi et al.[11]

Handgrip. Dynamic manual handgrip exercises were performed with an adjustable spring handgrip (Model LS3334; LIVEUP, Brazil) and prescribed from 40% of the 1 RM (repetitions maximum) test (3 sets of 20 contractions each per minute).[21]

Follow-up losses and intention-to-treat analysis

An attendance rate of 75% was considered. Patients who had three consecutive absences were discontinued from the program and considered as follow-up losses. A sensitivity analysis was performed for the follow-up losses according to the intention-to-treat principle.[22]

Data analysis

The descriptive analysis was presented as mean and 95% confidence interval for continuous variables and as frequency distribution and percentage for dichotomous variables. Normality distribution was performed using the Shapiro–Wilk test and variance homogeneity by the Levene test. Chi-square test was used to compare dichotomous variables. Paired Student's t-test was used in order to compare the pre- and post-training among the different groups, and the Wilcoxon test was used for the dynamometry variables, 2 cm mean radial velocity, 10 cm peak flow, 10 cm mean velocity, 20 cm peak flow and 20 cm mean velocity. Unpaired Student's t-test or Mann–Whitney U test were used to compare the intergroup training effect. Missing data regarding continuous variables were evaluated using the sensitivity analysis of the intention-to-treat principle according to the last observation method.[22] Cohen's d was used to determine the effect size of the main study variables after the interventions. Small ($d = 0.20$–0.49), average ($d = 0.50$–0.79) and large ($d = 0.80$–1.29) effect sizes were considered.[23] Tests were considered at a 5% significance level and performed in SPSS version 20.0 (Chicago, IL, USA).

Results

A total of 31 patients were evaluated, and 5 were excluded: 3 due to presenting large calibre vessels and/or individuals who performed heavy manual work, and 2 due to cognitive deficits resulting from the Mini–Mental State Examination (MMSE). The study started with 26 patients, and 4 of them did not complete it (1 death, 1 for an extended hospital stay period, 1 for financial difficulties, and 1 for AVF creation during the training period); however, all patients who started the training were analysed according to the intention-to-treat principle (Figure 1). The program was well tolerated by all patients in both groups, despite the need for adaptation in the first session after each weight load adjustment.

Regarding patients who initiated the protocol, 66.7% were male in the BFR and 71.4% were female in CG. The mean age was 61.33 ± 7.82 years and 60.14 ± 10.67 years for the BFR and CG, and body mass index (BMI) was 30.58 ± 5.91 kg/m^2 and 28.20 ± 6.72 kg/m^2, respectively. Left limbs were the most used for training (83.3% for BFR and 71.4% for CG).

All patients in the BFR group were hypertensive (100%) and the majority were diabetic (75%), while these occurrences were 64.3% and 21.4% for the CG, respectively. Of the patients, 75% in the BFR were in conservative stage 5 of CKD, while 64% of the CG were in stage 4 ($p = 0.045$).

The groups were comparable regarding laboratory tests as presented in Table 1.

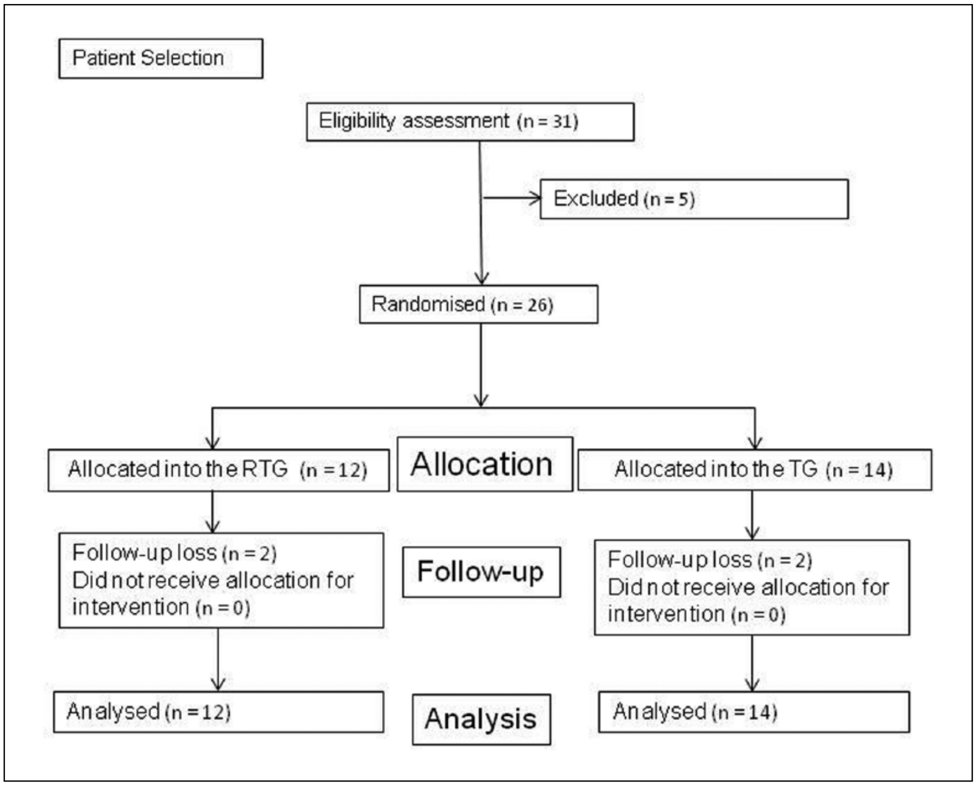

Figure 1. Flowchart of the clinical trial, according to the CONSORT.

Table 1. Initial laboratory characteristics of CKD patients by group.

Variables	BFR (n = 12)	CG (n = 14)	p value[a]
	Mean (95% CI)	Mean (95% CI)	
Urea (mg/dL)	102.20 (85.86–118.54)	127.97 (102.08–153.87)	0.092
Creatinine (mg/dL)	3.36 (2.89–3.82)	3.84 (2.73–5.15)	0.979*
Calcium (mg/dL)	8.82 (8.46–9.18)	9.13 (8.66–9.60)	0.263
Phosphorus (mg/dL)	3.79 (3.26–4.31)	4.28 (3.75–4.81)	0.216*
Sodium (mg/dL)	139.63 (137.65–141.61)	139.31 (136.76–141.86)	0.827
Potassium (mEq/L)	4.89 (4.50–5.27)	5.09 (4.59–5.59)	0.537
Haematocrit (%)	36.22 (33.05–39.39)	35.30 (32.16–38.43)	0.797*
Haemoglobin (g/dL)	12.20 (10.88–13.51)	11.41 (10.37–12.44)	0.315*
GFR CKD-EPI (mL/min)	18.51 (15.91–21.12)	15.17 (11.12–19.23)	0.147

BFR: blood flow restriction group; CG: control group; GFR CKD-EPI: glomerular filtration rate Chronic Kidney Disease Epidemiology Collaboration; CI: confidence interval.
[a]Student's t-test.
*Wilcoxon test.

Cephalic vein diameter

At the end of the study, an increase in cephalic vein diameter in the trained forearm in the BFR group was 0.20, 0.16 and 0.15 mm for the segments 2, 10 and 20 cm, respectively, and 0.24, 0.39 and 0.17 mm for CG, respectively. No differences between the groups were observed comparing the results after the intervention (Table 2). The training effect size was small for the segment at 2 cm (0.41) and average for the 10 and 20 cm segments (0.63 and 0.50, respectively) for the CG.

Cephalic vein distensibility

Cephalic vein distensibility increased 0.35 mm at the 2 cm segment for the CG at program end ($p = 0.020$). The gain in the other segments was not significant. No differences were found between the groups when comparing the final

Table 2. Intra and inter BFR and CG comparison regarding ultrasound, dynamometry and perimetry evaluations after training.

Variables	BFR group (n = 12) Mean (95% CI)			CG (n = 14) Mean (95% CI)			CBC p value[c]	p inter [d]
	Pre	Post	p intra[a]	Pre	Post	p intra[b]		
CV (2 cm)								
Diameter (mm)	2.50 (2.05–2.95)	2.70 (2.30–3.11)	0.160	2.71 (2.39–3.02)	2.94 (2.65–3.23)	0.008	0.411	0.438
Distensibility (mm)	2.55 (2.14–2.97)	2.69 (2.34–3.04)	0.350	2.62 (2.26–2.98)	2.97 (2.74–3.20)	0.020	0.803	0.318
CV (10 cm)								
Diameter (mm)	2.74 (2.16–3.32)	2.90 (2.30–3.50)	0.204	3.06 (2.61–3.51)	3.45 (3.01–3.88)	0.001	0.340	0.189
Distensibility (mm)	2.69 (2.00–3.15)	2.81 (2.35–3.27)	0.260	3.01 (2.36–3.66)	3.41 (2.94–3.88)	0.060	0.422	0.061
CV (20 cm)								
Diameter (mm)	2.95 (2.28–3.62)	3.10 (2.46–3.74)	0.332	3.40 (2.95–3.86)	3.57 (3.08–4.05)	0.237	0.226	0.206
Distensibility (mm)	3.05 (2.41–3.70)	2.90 (2.26–3.53)	0.258	3.20 (2.77–3.62)	3.52 (3.12–3.93)	0.061	0.699	0.074
RA (2 cm)								
Diameter	2.53 (2.21–2.85)	2.77 (2.50–3.04)	0.005	2.82 (2.55–3.10)	2.95 (2.64–3.26)	0.081	0.074	0.358
SPF (cm/s)	29.52 (20.57–38.46)	30.06 (20.26–39.86)	0.868	34.84 (27.17–42.52)	35.30 (30.62–39.98)	0.902	0.332	0.279
MV (cm/s)	6.93 (3.71–10.14)	7.89 (4.14–11.65)	0.538	8.88 (4.61–13.14)	10.13 (7.04–13.23)	0.530	0.355	0.321
RA (10 cm)								
Diameter	2.59 (2.21–2.96)	2.85 (2.42–3.29)	0.021	2.90 (2.62–3.17)	3.02 (2.75–3.29)	0.017	0.139	0.205
SPF (cm/s)	25.18 (18.19–32.17)	27.62 (18.50–36.75)	0.388	29.81 (23.36–36.27)	31.93 (27.17–36.69)	0.404	0.280	0.150
MV (cm/s)	5.71 (2.86–8.57)	6.27 (3.80–8.75)	0.721	7.22 (4.53–9.92)	7.75 (5.08–10.42)	0.766	0.258	0.393
RA (20 cm)								
Diameter	2.93 (2.46–3.39)	3.11 (2.69–3.53)	0.018	3.03 (2.61–3.45)	3.34 (3.05–3.63)	0.026	0.724	0.331
SPF (cm/s)	24.27 (18.93–29.61)	32.43 (18.34–46.52)	0.139	34.58 (23.43–45.74)	36.03 (26.47–45.59)	0.759	0.100	0.341
MV (cm/s)	4.59 (2.63–6.54)	12.21 (–3.68–28.12)	0.575	7.31 (4.47–10.14)	9.66 (5.44–13.88)	0.390	0.123	0.258
Physical examination								
Perimetry (cm)	26.27 (24.87–27.67)	26.49 (25.13–27.85)	0.228	25.62 (23.67–27.56)	25.84 (24.11–27.57)	0.216	0.571	0.538
Dynamometry (kgf)	26.83 (21.18–32.48)	29.08 (23.86–34.30)	0.060	24.93 (19.76–30.10)	27.29 (22.11–32.46)	0.003	0.394	0.302

CBC: comparison of baseline characteristics; RA: radial artery; CV: cephalic vein; SPF: systolic peak flow; MV: mean velocity.
[a]Paired Student's t-test.
[b]Wilcoxon test.
[c]t-test for independent samples.
[d]Mann–Whitney.

training results (Table 2). The training effect size was considered average for all segments for the group without restriction (CG; 0.58, 0.77 and 0.72, respectively).

Radial artery diameter

Radial artery diameter increased in the three segments for the BFR, while this increase was only observed for the 10 and 20 cm segments of the CG, as shown in Table 2. No differences were found when comparing post-training measures. The training effect size for CG was small in all three evaluated segments (0.36, 0.27 and 0.38, respectively).

Radial artery flow peak and mean flow velocity

No changes were observed for systolic peak flow or mean velocity in either group (Table 2). The effect size was considered small or insignificant in all variables for the group that did not use BFR in the studied segments.

Handgrip strength and forearm circumference

Handgrip strength increased in 81.82% (18 out of 22) of the patients who completed the training; however, this gain only occurred for the CG. No differences were observed when the final measures were compared (Table 2). The training effect was small (0.21) for the group that used BFR.

Forearm circumference showed no changes between groups, nor when post-intervention measures between groups were performed (Table 2). The group that used BFR presented small advantage (0.25) regarding the training effect.

Discussion

This is the first study to use an association between physical training and BFR for forearm muscles in CKD patients with AVF indication. Both groups had increased vessel diameters after training; however, no differences were found between them when the final outcomes of each group were compared.

An increase in cephalic vein diameter after training was found in the proximal segments (20 cm) in the group that performed training without BFR.

An increase in the radial artery diameter was observed in all segments evaluated in the BFR group, but this increase was only observed in the distal segments of the group that performed the training without the restriction. Handgrip strength increased for the group without BFR. No changes in flow or superiority in the use of BFR were observed in relation to conventional training.

This study used 50% of the systolic blood pressure value and 40% of the maximum voluntary contraction (MVC) for prescribing BFR training, but perhaps this value was insufficient to produce greater gains in comparison to conventional training. One study used three different levels of BFR in healthy individuals and found maximized acute responses when the training was developed with pressures of 40% and 50% arterial occlusion and 30% of MVC;[20] however, no changes were observed when occlusion was used at 60%.

Cephalic vein diameter

An increased cephalic vein diameter was observed in the group that performed training without BFR, similar to that found in the study by Rus et al.,[10] Kumar et al.[18] and Uy et al.,[6] with the latter performing the training before AVF creation.

Our results corroborate the findings by Tinken et al.,[23] who verified that prolonged training with vascular occlusion can reduce adaptations resulting from physical training, presenting a significant increase using the same protocol without BFR.

Another point regarding the results obtained in the BFR group is the presence of hypertension and diabetes mellitus in the vast majority of patients in this group. We are aware that an increase in glycosylated haemoglobin in diabetes results in increased superoxide anion generation, negatively influencing nitric oxide (NO) action.[24] Henning and Chow[25] suggest that lipid peroxidation products (lipid hydroperoxides) directly attack endothelial cells and cause membrane dysfunction. These pathologies are present in most CKD patients, being associated with increased oxidative stress and impaired endothelial cell function.[26]

Vein distensibility

No difference was observed between the two groups at the end of the training, with no increase in distensibility for the BFR group. The distal segment (2 and 10 cm) diameter increase in the forearm of the group without BFR can be attributed to mean pre-training values in this segment, which were below those recommended for AVF creation,[5] unlike the behaviour observed in more proximal regions of the forearm (20 cm), which did not change after training due to presenting higher calibres.

Radial artery diameter

The increase in radial artery diameter in the three BFR group segments occurred similarly to the study by Rus et al.,[10] although these authors only used isometric exercise without BFR. These same authors found no changes in arterial diameter performing intermittent compression in CKD patients undergoing a haemodialysis program in another study.[27]

The association between exercise and BFR was effective for increasing radial artery diameter, and this effect may have been due to reactive hyperaemia caused by forearm occlusion during exercise, leading to endothelium-dependent flow-mediated dilatation.[28] Another aspect to be considered is the onset of turbulent flow in the vessel, which may have provided an increase in shear stress, followed by increased deposition of NO produced by the endothelium and leading to an increase in its diameter due to wall dilatation by NO deposition.[25]

This increase was observed in the proximal segments (20 cm) in the group without BFR, possibly because isometric exercise may favour greater blood flow concentration in the wrist flexor muscle fibres located in the proximal third of the forearm where the muscle fibres are concentrated.[29]

Another aspect in relation to the BFR exercise is the rapid muscle fibre recruitment compared to conventional training[30] and using low-intensity loads, which produce similar results using heavier loads.[20]

Radial artery flow peak and mean flow velocity

Similar to the study by Rus et al.,[10] no changes in flow were observed for any of the studied groups. Lockhart et al.[31] reported that the increase in arterial flow is important for the success of the AVF. Our study observed an increase in all diameters of the radial artery in the group that underwent training with BFR; however, this increase was not accompanied by significant improvement in blood flow.

Handgrip strength

Handgrip strength was higher for the group without the restriction. One possible explanation can be attributed to the fact that an association of BFR with low-intensity training provides the same gains as conventional strength training using higher loads.[20,32] Training without BFR seems more appropriate for CKD patients, since they do not tolerate higher intensity exercise programs well and present reduced muscle mass, they were aggravated by the disease stage and they may consequently achieve lower gains at the end of a training program compared to healthy individuals.[33]

Another aspect to be considered is there were more males in the restriction training group, unlike in the CG. Men have larger muscle fibres and higher upper body strength compared to women.[34] The higher strength gains in the unrestrained group (mostly women) may have occurred as a result of training, equating the muscle strength already present in men.

Forearm circumference

Regarding forearm circumference, no changes were observed at the end of the training. This is unlike the studies by Rus et al.[10] and Kong et al.[19] in which an increase was found. However, it is noteworthy that the first study used isometric exercises without flow restriction, while the latter was performed in patients who already had AVF.

Safety of using BFR during training

No complaints or complications from using BFR were reported during the training period in the BFR group, although literature reports[12] subcutaneous haematomas/bruising in the cuff location, numbness, dizziness, and venous thrombosis in different studied populations.

Clinical considerations regarding BFR

The use of BFR associated with exercise was effective in increasing the radial artery diameter, while conventional exercises proved to be more effective for cephalic vein and handgrip strength. We must take into account the initial characteristics of these vessels before AVF creation, so training programs with or without BFR can be better defined and applied.

Although we have not objectively evaluated the diameter of the vein at the site of the tensiometer, future studies need to observe this registry in order to provide evidence about the existence of some potential damage to the cephalic vein.

Limitations

Follow-up losses throughout the study demonstrated the severity of patients with indication for AVF creation, implying hospitalization, AVF creation before the end of the study and deaths due to clinical complications, resulting in fewer participants in the study. Incompatibility between the groups in relation to gender and comorbidities was a result of the small sample size.

Conclusion

Physical training increased cephalic vein diameters in both groups; however, the addition of BFR showed no significant additional benefit. The addition of BFR promoted a significant increase of radial artery diameters in relation to the CG. The physical training impact with or without BFR on AVF maturation remains to be determined.

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Declaration of conflicting interests

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