

# Photobiomodulation therapy combined to static magnetic field before blood flow restriction training in untrained individuals: protocol for a double-blind, randomized, placebo-controlled trial

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## ABSTRACT

**Background:** Photobiomodulation therapy with static magnetic field (PBMT/sMF) stands out for being a non-pharmacological resource with bioenergetic effects capable of accelerating muscle recovery, delaying muscle fatigue and potentiate gains in different training protocols. In recent years, blood flow restriction (BFR) associated with low load exercise (20-30% 1RM/MVC) has demonstrated positive effects on muscle performance. However, the effects of PBMT/sMF combined with BFR training are still unknown. **Objective:** Verify the effects of PBMT/sMF associated with BFR training and compared with high load training (HLT) in the muscle strength, muscle damage, inflammation, and the oxidative stress. **Methods:** This is a protocol of a randomized, double-blind, placebo-controlled clinical trial. The participants will be healthy men between the ages of 18 to 40 years, with no practice in upper limb strength training in the previous three months. The volunteers will be randomly divided into four groups: (1) PBMT/sMF + BFR; (2) PBMT/sMF + HLT; (3) placebo + BFR; (4) placebo + HLT. The PBMT/sMF will be applied immediately before strengthening protocol (4 sets x 20 repetitions of elbow flexion). The BFR groups will undergo to exercise with low load (30% of MVC), while the HLT groups will performed the same protocol with 80 % of MVC. The primary outcome will be muscle strength, measured in baseline, fourth, eighth week of training and detraining period. The secondary outcomes include measured the fatigue resistance, arm circumference, muscle damage, inflammatory and oxidative stress levels in one session, during, after intervention and detraining. **Discuss:** This trial will elucidate the effects of PBMT/sMF when used in association with BFR training or HLT.

**Keywords:** Phototherapy; Muscle performance; Occlusion vascular; Oxidative stress; Exercise.

## BACKGROUND

The resistance exercise (RE) is an important method used for prevention, rehabilitation, maintenance of health, and quality of life, increasing practitioners' number, regardless of age or sex.<sup>(1,2)</sup> These individuals aim to achieve through RE benefits such as increased strength, muscle mass, and sports performance.<sup>(3)</sup> RE with high load training (HLT) appears as the most effective method for developing muscle strength, and, since the last two decades it has been a field of increasing research due your beneficial effects in health human. It is known, the RE entail a systemic change in the body through physiological adaptations in anaerobic and aerobic metabolism, changing the neuromuscular system, increasing muscles fibers numbers, and inducing muscle hypertrophy.<sup>(2-4)</sup>

The American College Sports Medicine (ACSM) and other authors recommend that in order to achieve significant muscle strength gain and hypertrophy, a load greater than 70% of a maximum repetition (1RM) or maximal voluntary contraction (MVC) should be used.<sup>(5,6)</sup> Unlike several types of RE that used high intensity (70% -85%), blood flow restriction (BFR) training with low load (20-50% 1RM or MVC), called Kaatsu training, stands out.<sup>(7)</sup> This training method showed positive results, as increased

muscle strength and mass, similar to high-load training (HLT), so much in adults,<sup>(8,9)</sup> elderly,<sup>(10-12)</sup> and athletes.<sup>(13,14)</sup>

One of RE's effects due to intensity use and repetitive of musculature is muscle fatigue, being responsible for a progressive decline in performance. Muscle fatigue also contributes to muscle damage, which corresponds to an inflammatory response, with an increase in blood muscle proteins and delayed onset muscle soreness.<sup>(15-17)</sup> Due to the growing scientific interest in the search for resistance in exercise, scientists have been studying ways to measure muscle damage induced by exercise. Therefore, measurements of the activity of the enzyme creatine kinase (CK) have been used to determine muscle damage and recovery process.<sup>(17,18)</sup>

Some authors pinpoint that the BFR training possibly induces fatigue earlier than HLT due to your metabolic stress, caused by local hypoxic on muscle<sup>(19)</sup>. Metabolic stress is currently known as a physiological process that occurs during exercise in response to low energy that leads to metabolite accumulation [lactate, phosphate inorganic (Pi), and ions of hydrogen (H+)] in muscle cells.<sup>(9,20)</sup> The metabolic stress can produce Oxigen-reactive species (ROS), which at moderate antioxidant capacity and immune response<sup>(21)</sup>.

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Recent studies showed that BFR effects had shown an increase in the cytokine IL-6, which plays a role in skeletal muscle remodeling<sup>(20)</sup>. This associated response is associated with the hypoxic muscle environment generated by BFR and ROS production, contributing to the increased demand for energy production by anaerobic metabolism and glycogen depletion<sup>(12,20)</sup>. However, studies investigating whether BFR can modulate acutely, and chronically the antioxidant and inflammatory responses present controversial results. In addition, lack of detailed information on BFR application, exercise protocol, small sample size and data loss affect the reliability of the results and result in a high risk of bias. The scarcity of clinical trials with reliable results and high methodological quality demonstrates the need for further studies on the topic to elucidate the effects of BFR on oxidative stress and ROS production.

More recently, Vanin et al<sup>(22)</sup> also shown that PBMT/sMF can potentiate gains in different training protocols, such as strength training. The PBMT is defined as a light therapy that uses non-ionizing light sources, such as lasers, light-emitting diodes (LEDs), and broadband light, from the visible to the infrared spectrum.<sup>(23)</sup> Recent evidences have shown that PBMT can positively affect the antioxidant activity and improve musculoskeletal conditions<sup>(24-27)</sup>. In addition, PBMT has been used in combination with a static magnetic field (sMF)<sup>(28)</sup>, generating better effects on cell metabolism.<sup>(29)</sup> Although PBMT or PBMT/sMF has considerably increased the number of searches in recent years, most studies have evaluated only PBMT/ sMF acute effects<sup>(27)</sup>. However, the effects of PBMT/sMF therapy combined with BFR training on muscle performance and biochemical responses have not yet been investigated.

The purpose of this study is to evaluate the effects of PBMT/sMF with BFR training in muscle performance. Thus, this clinical trial will test the hypothesis that the combination of PBMT/ sMF with BFR may be an approach capable of providing adaptations of the skeletal musculature, the redox system, and the inflammatory response, with a consequent increase in muscle performance.

## METHODS

This is a prospectively registered, four-arm randomized placebo-controlled trial with concealed allocation, blinded measurers and volunteers, intention-to-treat analysis, and

one month of follow-up (detraining period). All the study components will be completed at the Sports Medicine Institute (SMI). The study follows the SPIRIT (Standard Protocol Items: Recommendations for International Trials) 2013 checklist<sup>(30)</sup> (Additional file 1) and the TIDieR (Template for Intervention Description and Replication)<sup>(31)</sup>.

## Ethical aspects

The study was approved by the Ethics Committee of the University Center UNICNEC. Following the Declaration of Helsinki, all volunteers were advised about the procedure and signed informed consent before participation in the study (CAEE 09865119.7.000.5571). This trial is registered in the Register of Brazilian Clinical Trials (REBEC), number RBR-3623xj. The volunteers will then be informed about the procedures and will sign a statement of informed consent in compliance with Resolution 196/96 of the Brazilian National Board of Health before the execution of the study. All personal data will be confidential.

## Participants

For recruitment of volunteers, initial contact will be made through social media, afterward, the volunteers will be solicited to appear at Institute of Sports Medicine (IME), the research team will ask about their personal data to identify if they meet the inclusion criteria or if they need to be excluded from the clinical trial. A questionnaire will be administered addressing age (years), body mass (kilograms), height (centimeters), not dominant upper limb, schooling (no schooling, elementary school education, high school education, university education, or postgraduate degree), and marital status (single, married or widowed).

## Eligibility Criteria

Pre-defined inclusion criteria will be employed (1) healthy individuals, (2) male, (3) age between 18 - 40 years, (4) do not be realizing resistance training in the previous three months. The voluntaries with the following characteristics will be excluded from the study, (1) history of musculoskeletal injury to the upper limb, (2) history of surgical, (3) history of cardiovascular pathology, (4) history of venous thrombosis and (5) use of pharmacological agents or nutritional supplements. Subjects who discontinue participation in the study will be invited to participate in the assessment three months after



the start of treatment (week twelfth of the study). Thus, all individuals will be included in the intention-to-treat analysis. Adherence to treatment will be assessed by calculating the percentage of sessions completed by each volunteer. Patients will be instructed not to drink alcohol or food before training sessions. If the patient has a fever or malaise session, he will be asked to reschedule the session.

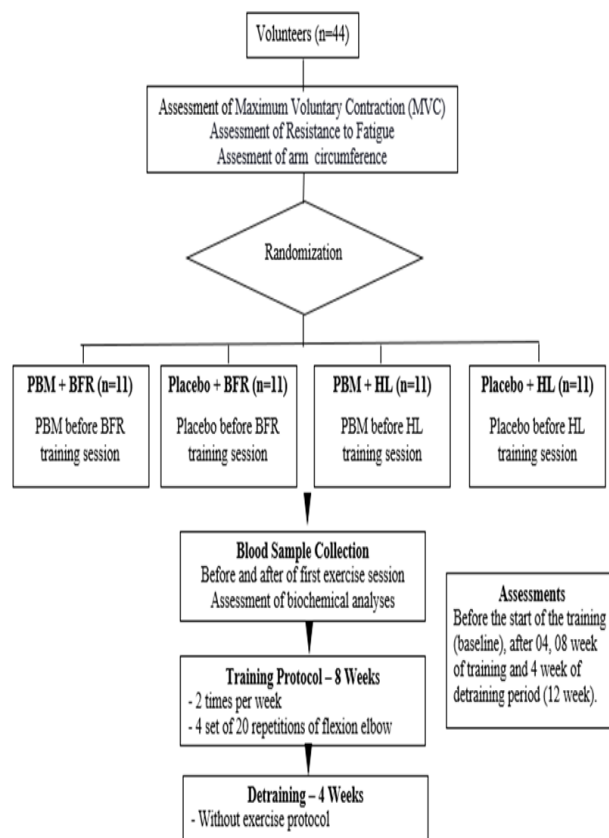
### Randomization and Blinding

Seeking to minimize selection bias and ensure that all volunteers will be randomly allocated to any group, the block randomization will be performed by a researcher who will not have contact with the study subjects or other researchers involved in the project.

Another researcher will be responsible for programming the device (PBMT/sMF or placebo) and will be instructed not to inform volunteers or other researchers about the type of treatment (PBMT/sMF or placebo). The sounds and signals emitted by the device, as well as the information displayed on the screen, were identical, regardless of the type of treatment (PBMT/sMF or placebo), providing adequate concealment by volunteers and therapists. All volunteers will be used a blindfold during treatments, both for safety and to help blind them. Thus, volunteers and evaluators were blinded to maintain the double-blind design. Randomization tags will be created at [www.randomization.com](http://www.randomization.com), and a series of sealed, opaque, and numbered envelopes will be used to ensure confidentiality and to determine which experimental group each volunteer will be allocated. Volunteers will be allocated as reported below:

- (1) PBMT/sMF + BFR: PBMT/sMF before the BFR training sessions;
- (2) PBMT/sMF + HLT: PBMT/sMF before the HLT sessions;
- (3) placebo + BFR: placebo before the BFR training sessions;
- (4) placebo + HLT: placebo before the HLT training sessions.

The evaluations will be performed before starting the protocol (baseline) and after four, eight weeks of sessions training, and one month of follow-up (detraining period). The blood samples and biochemical analyses evaluation will happen in the first training session (1 min - before and after) in all groups to verify the acute effects. A flow chart that summarizes the procedures that will be performed in this study is shown in Figure 1. Study design schedule in accordance with the SPIRIT checklist is showed in Painting 1.



**Figure 1.** Flow diagram

**Note:** BFR, blood flow restriction, PBM, photobiomodulation therapy, HL= high load.

### Interventions

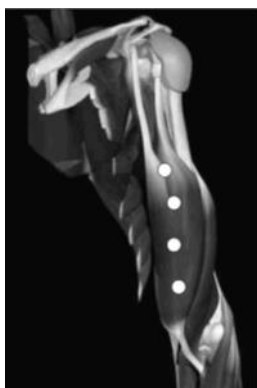
#### Training session

Training sessions will be held at a 48-hour interval between each session. Upon arrival the volunteers will be submitted to a warm-up period of 5 min the ergometer cycle (Acte Sports, São Paulo, Brazil). Later the volunteers will be led and actively submitted to PBMT/ sMF or placebo in both upper limbs. After this, the subject will perform the training protocol focused on the biceps brachii muscle. All volunteers will be instructed not to eat any food one hour before training, alcoholic drink and caffeine. The adverse events will be monitoring during all sessions and collated, and exercise may cause red spots, redness, pain, and discomfort in the upper limbs during or after exercise sessions. These symptoms will not be considered adverse effects. There may be discomfort due to blood collection; however, in order to minimize discomfort, an experienced nurse will perform the collection. We define adverse events as cases in which dizziness occurs, tingling/paresthesia in the upper limb, bruising, during or after training. If one of the volunteers has these symptoms, the training session will be stopped immediately.



**Table 1.** Parameters for Activ Pro® device.

Class	1M
<b>Number of lasers</b>	1 Super-pulsed infrared
Wavelength (nm)	905 ( $\pm 1$ )
Frequency (Hz)	250
Peak power (W)	50
Average mean optical output (mW)	1.25
Power density (mW/cm <sup>2</sup> )	2.84
Energy density (J/cm <sup>2</sup> )	0.085
Dose (J)	0.0375
Spot size of laser (cm <sup>2</sup> )	0.44
<b>Number of red LEDs</b>	3 Red
Wavelength of red LEDs (nm)	640 ( $\pm 10$ )
Frequency (Hz)	2
Average optical output (mW) – each	66.67
Power density (mW/cm <sup>2</sup> ) – each	74.08
Energy density (J/cm <sup>2</sup> ) – each	2.22
Dose (J) – each	2.00
Spot size of red LED (cm <sup>2</sup> ) – each	0.9
<b>Number of infrared LEDs</b>	3 Infrared
Wavelength of infrared LEDs (nm)	875 ( $\pm 10$ )
Frequency (Hz)	16
Average optical output (mW) – each	83.33
Power density (mW/cm <sup>2</sup> ) – each	92.59
Energy density (J/cm <sup>2</sup> ) – each	2.77
Dose (J) – each	2.50
Spot Size of LED (cm <sup>2</sup> ) – each	0.9
<b>Magnetic Field (mT)</b>	35
Irradiation time per site (sec)	60
Total energy irradiated per site (J)	13.5375
Number of sites irradiated per treatment	4
Total energy irradiated per treatment (J)	54.15
Aperture of the device (cm <sup>2</sup> )	4
Application mode	Cluster probe held stationary in skin contact with a 90-degree angle and slight pressure

**Figure 2.** Point of application PBMT/sMF**Table 2.** Cuff pressures during protocol exercise

Cuff Pressure	(Week.Session)
120 mmHg	1.1 – 1.2 – 2.1 – 2.2
130 mmHg	3.1 – 3.2 – 4.1 – 4.2
120 mmHg	5.1 – 5.2 – 6.1 – 6.2
130 mmHg	7.1 – 7.2 – 8.1 – 8.2

eight weeks, totaling 16 sessions. The exercise that will be proposed is Scott elbow flexion unilaterally, with a 30% MVC pre-assessment load for BFR groups and 80% MVC for HLT groups. During the fourth week the load will be adjusted, and thus the value of 30% of the MVC of the assessment that occurred at the end of the fourth week will be used.

The BFR protocol will consist of four sets of 20 repetitions or until failure with a rest interval of 30 seconds between sets, being stimulated with the standard verbal command for all voluntaries in BFR groups. For to HLT group the participants will be submitted three sets with 10 repetitions. Rest periods between set will be one minute. The execution speed in BFR and HLT groups will be controlled by a metronome set at three seconds, which was equally divided between concentric and eccentric muscle action. This process will be realized for a physical therapy and the duration of each session of exercise will be between 5 to 6 minutes.

### Outcomes Measures

#### **Maximum Voluntary Contraction (MVC) and Muscle Fatigue Induction Protocol (MFIP)**

The protocol for determining muscle strength used the maximum voluntary contraction (MVC) capacity and endurance will be followed by a blind researcher (a trained physiotherapist of Sports Medicine Institute) and will occur on the Biodex 4 Pro System isokinetic dynamometer (Biodex Medical Systems, USA). The positioning of the equipment in the equipment will be performed according to the manufacturer's instructions for the evaluation of the forearm flexion movements. As the tests will be performed unilaterally (non-dominant arm) and the positioning of the equipment will remain the same in all evolutions for each volunteer.

The first part of the isokinetic dynamometer protocol is to determine the maximum isometric torque of the elbow flexors (biceps brachii). To this end, three voluntary contractions (VC) will be performed in the isometric mode at the 45 ° elbow flexion position, lasting 5s and a 5s interval between contractions. During VCs, a constant and standardized verbal stimulus will be performed by the researchers. The highest isometric torque value achieved in the VCs will be considered the



maximum voluntary contraction (MVC). After the determination of MVC, a period of 180 seconds will be respected before the initiation of the muscle fatigue induction protocol (MFIP) to verify the resistance to fatigue.

The MFIP will consist of a set of 20 concentric/eccentric elbow flexor contractions. Contractions will be performed at 90° amplitude and 90° .sec<sup>-1</sup> velocity for eccentric contractions and 60° .sec<sup>-1</sup> for concentric contractions. The guidance provided to the volunteers was to employ the highest strength possible to execute the elbow flexion movement and resist the elbow extension movement imposed by the dynamometer from the first to the last repetition.

### Arm circumference

A researcher (physical therapy) previously trained and blinded to the experimental and placebo groups will evaluate arm circumference as follows, with free upper limb thus discarding the possibility that garments will increase and influence the result. With the patient in a sitting position, the researcher will ask the volunteer to move away from the upper limb of the trunk and thus will circumvent the upper limb in five, ten and 15 centimeters above the reference point (lateral epicondyle of the humerus), with the tape measure to evaluate the circumference of this limb.

### Blood samples and biochemical analyses

A nurse will be responsible to blood collection and won't be informed about groups randomization, blood samples (10 ml) will be collected from the antecubital vein before and 1 minute after the exercise protocol. Blood samples will also be collected 1 minute after the protocol. The samples will be taken by a nurse blinded to the allocation of the volunteers to the four experimental groups. One hour after collection, each sample will be centrifuged at 3600 rpm for 10 minutes. Pipettes will be used to transfer the serum to Eppendorf® tubes (Eppendorf, Hamburg, Germany), which will be stored at -80°C until analysis.

Blood analysis will involve the determination of CK activity as indirect marker of muscle damage, using spectrophotometry and specific reagent kits (Labtest Diagnóstica, Lagoa Santa, MG, Brazil); IL-6 and TNF- $\alpha$  levels as inflammatory markers, using ELISA and specific reagents (R&D Systems, Minneapolis, MN, USA); and thiobarbituric acid reactive substances (TBARS), carbonylated proteins, catalase (CAT), superoxide dismutase (SOD), and total antioxidant capacity (TAC) as

markers of oxidative stress, using spectrophotometry and specific reactions.

### Data Analysis

#### Calculation of sample size

For sample calculation, the value of  $\beta$  will be considered to be 20% and  $\alpha$  of 5%. The total number of volunteers in the survey was calculated based on data presented by De Marchi et al.<sup>(33)</sup> The author conducted a study to analyse the effects of PBMT on the performance of futsal players and recovery in an uncontrolled field environment, taking into account the effect size of 0.65 found in the results obtained in this study. Using these data for sample calculation (using Gpower 3.1), we obtained as a result n from 44 volunteers (final sample, excluding possible losses).

#### Statistical Analysis

The statistical analysis it will be conducted following intention-to-treat principles (i.e., the volunteers it will be analyzed in the groups to which they were allocated). Data normality it will be tested by Kolmogorov-Smirnov test. If the data shows normal distribution, two-way repeated measures analysis of variance with post hoc Bonferroni correction will be realized. If the data do not show a normal distribution (non-parametric) will be analyzed using the Friedman test and, secondarily, the Wilcoxon signed-rank test. The association between categorical variables will be analyzed using the Chi-square test or Fisher's exact test. Data will be expressed as mean and standard deviation, mean difference between treatments, and 95% confidence intervals (95% CIs). Data will be also expressed as frequency (%). The significance level was set at  $p < 0.05$ . The magnitude of differences (Cohen-d) between groups, to examine practical significances, was calculated using the mean and SD of placebo, PBMT-sMF and BFR treatments (using Gpower 3.1). We adopted the criteria of Cohen for the analysis (0.2: small; 0.50: moderate; 0.80: large). All analyses will be calculated one of the researchers who be not involved in data collection.

## DISCUSSION

In the proposed study, the effects of the BFR associated with PBMT/sMF will be identified and compared with the effects of BFR training, HLT, both in separated form and associated with previous application of PBMT/sMF on muscle performance (strength fatigue resistance). Moreover, the acute (one session) and long-term



effects (eight weeks) of the training protocol on markers inflammation, oxidative stress, muscle damage will be verified to determine the changes occurred in each intervention.

This will be the first study to evaluate the acute, long-term effects of BFR and PBMT / sMF isolated and combined on indirect exercise-induced oxidative stress. It is currently known that production of reactive oxygen species (ROS) plays a vital role in cell function in terms of acting as a signaling molecule<sup>(34)</sup>. In addition, ROS play an important role in regulating muscle strength production and adaptive responses induced by exercise training<sup>(34,35)</sup>. On the other hand, a systemic overproduction of ROS in skeletal muscle promotes an interruption of signaling and redox control, which can damage cellular components (lipids, proteins and DNA), cell dysfunction and even cause apoptosis<sup>(34)</sup>. Furthermore, the increase in ROS can elevate the levels of pro-inflammatory cytokines and, consequently, cause contractile dysfunction, fatigue and decreased performance. The implication of this redox imbalance is a longer period of muscle recovery, therefore, impairing the quality of training sessions and exercise-induced adaptive response.<sup>(36)</sup> This is a fundamental issue, especially for subjects exposed to periods of intense training and in the musculoskeletal rehabilitation process. Thus, this study has a relevant impact on clinical practice, as it will demonstrate whether the application of PBMT/sMF with BFR can be feasible for healthy and unhealthy patients, as well as elucidating the possible mechanisms responsible for its effects.

In addition, we will investigate the effects of a period of physical activity interruption, that is, a period of detraining. As strengths of this study, we can highlight that it has high methodological quality because it is randomized and prospectively registered, masks the evaluators and patients, conceals allocation, and uses an intention-to-treat approach. We also calculated sample size in order to provide adequate statistical power to identify possible differences in the main outcomes.

The limitations of study are the use the circumference of arm to evaluation the muscle volume trough brachii biceps and not magnetic resonance image. However, in clinical practice, the circumference of arm is the most used method for assessing muscle volume due to its cost-benefit and easy application, presenting quantitative results<sup>(37)</sup>. The selection criteria of the study exclude women and the voluntaries are only male, this occurred so that there was no

influence of the woman's menstrual cycle; once there was biochemical analysis of biomarkers of muscle damage and oxidative stress. The results from this study will be disseminated through scientific publications in international peer-reviewed journals and presentations at national and international scientific meetings.

**Authors' contributions:** All cited authors participated in these steps. JVF: Conceptualization, Methodology, Project Administration, Visualization, Writing. TDM: Conceptualization, Methodology, Formal Analysis, Validation, Supervision, Writing. ECPLJ and MS: Validation, Supervision, Writing. All authors have read and approved the final version of the manuscript.

**Conflict of interest:** Professor Ernesto Cesar Pinto Leal-Junior receives research support from Multi Radiance Medical (Solon, OH - USA), a laser device manufacturer. Multi Radiance Medical had no role in the planning of this study. They had no influence on study design, data collection and analysis, decision to publish, or preparation of the manuscript. The remaining authors declare that they have no conflict of interest.

**Transparency statement:** The JVF affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained".

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