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# Acute effects of the resistance exercise associated with different blood flow restriction pressures on bone remodeling biomarkers

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ABSTRACT

*Background:* The present study analyzed the acute responses of parathyroid hormone (PTH) and bone-specific alkaline phosphatase (BSAP) to the low-intensity resistance exercise with blood flow restriction using different occlusion pressures.
*Methods:* Twelve women completed the three protocols of this crossover study: resistance exercise without blood flow restriction (RE), resistance exercise with blood flow restriction and occlusion pressure corresponding to 70% of systolic blood pressure (RE + BFR70), and resistance exercise with blood flow restriction and occlusion pressure corresponding 130% of systolic blood pressure (RE + BFR130). All exercises were performed in a guided squat apparatus with load corresponded to 30% of one-repetition maximum test.
*Results:* Relative to resting levels, PTH concentrations decreased significantly ($p = .000$) post-exercise in all groups and increased significantly ($p = .000$) 15 min post-exercise in RE + BFR70 and RE + BFR130 groups; PTH concentrations returned to resting levels after the 30-min recovery period in all groups. There was no significant difference ($p > .05$) between BSAP values at rest and 30 min post-exercise.
*Conclusion:* In conclusion, our results showed that protocols with blood flow restriction using occlusion pressures equivalent to 70% and 130% of systolic blood pressure were more effective than RE alone to induce PTH peaks, and to promote a metabolic condition favorable to bone anabolism.


## 1. Introduction

Osteoporosis is characterized by a decrease in bone mineral density to levels below normal and is associated with alterations in bone micro-architecture that increase bone fragility and susceptibility to fractures.[1] According to Jonston e Dagar,[2] osteoporosis is not only associated with an increased risk of fractures, but also with an increase in chronic pain, depression, deformities, loss of independence and even death.

Bone metabolism is regulated by a series of hormones that can be monitored as biomarkers of bone health. Among them, parathyroid hormone (PTH) is one of the main regulators of extracellular calcium levels via calcium reabsorption in bones.[3–5] Several studies have shown that high PTH concentrations for long periods are related to bone catabolism, whereas peaks of PTH promote bone anabolism.[3,6] Therefore, exogenous administration of PTH to promote peaks throughout the day has become one of the main treatments for osteoporosis.[7–9] The main mechanisms involved in PTH's anabolic effects include its anti-apoptotic and proliferative effect on osteoblasts (mediated by insulin-like growth factor - IGF), conversion of bone lining cells to osteoblasts, and suppression of sclerotin expression in contributing osteoblasts for its formation and differentiation, among other factors.[7]

Bone-specific alkaline phosphatase (BSAP) is another important biomarker of bone metabolism,[10] because of its association with bone formation and interaction with osteoblasts.[11,12] This interaction has effects on osteoblast activity, i.e., the higher the concentration of BSAP, the higher the activity of osteoblasts.[13]

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A non-pharmacological alternative to the treatment of osteoporosis is physical exercise. In general, physical activity and exercise have been reported as key factors in bone remodeling.[12,14–16] Protocols involving resistance exercise (RE) have shown important effects on bone metabolism biomarkers, such as BSAP and PTH.[17]

Although the positive effects of RE on bone metabolism are well described in the literature, not all individuals benefit from this practice, since satisfactory results on bone remodeling have been associated with high-intensity exercises.[16–20] Populations with skeletal muscle limitations or reduced functional capacity, such as elderly and individuals with degenerative diseases, have a low or, in many cases, no tolerance to moderate- or high-intensity exercises,[21] that is, exercises with loads greater than 70% of one maximum repetition (1-RM).

Alternatively, blood flow restriction (BFR) associated with low intensity RE (30–40% 1-RM), has been shown to be effective in the treatment of arterial hypertension,[22] and to promote increases in muscle strength and hypertrophy.[23]Similarly, the mechanical overload, BFR associated with low intensity RE may have a positive effect on bone metabolism.[24–26]

Although several studies involving RE and BFR with different occlusion pressures have been published in the specialized literature,[21,27–29] there is still no evidence to support the choice of a higher or lower occlusion pressure, especially in relation to protocols intended to produce improvements in bone metabolism. Therefore, this study analyzed the acute responses of PTH and BSAP to the strength exercise with blood flow restriction using different occlusion pressures.

Our hypothesis is that blood flow restriction can promote positive changes in bone remodeling biomarkers, promoting a favorable condition for bone formation.

## 2. Methods

### 2.1. Participants

Twelve female university students (age: 21.75 ± 1.96 years; body mass: 61.84 ± 11.85 kg, height, 162.73 ± 5.83 cm) completed two familiarization session and three experimental protocols over four consecutive weeks. Physically inactive women (who were not involved in exercise programs in the three months prior to data collection) and who did not have a diagnosis of chronic disease or disease related to bone metabolism were included in the study. Participants who did not attend any of the data collection stages were excluded.

The sample size was calculated considering a statistical power of 80%, a significance level of 5% (two-tailed), an average standard deviation of eight units for the main outcome variable (parathormone) based on the study by Maimoun et al.[30] who evaluated the acute responses of bone remodeling biomarkers to exercise. The sample size needed to detect a minimal difference between treatments of five units was 12 participants. Considering a sample loss of 20%, the initial sample size was 14 subjects. During the study, two subjects were excluded for not attending one of the data collection stages (due to professional commitments), thus, the final size of the final sample was twelve subjects.

To calculate the sample size, an online calculator for cross-over design studies was used (http://hedwig.mgh.harvard.edu/sample_size/).

### 2.2. Study design

This study used a crossover design, in which subjects were randomized to two blocks containing all experimental protocols applied in a different order in each block. All participants were familiarized with the experimental protocol, in two sessions 48 h apart, in which they tried the exercise protocols and the use of pneumatic tourniquets for BFR. At the end of the familiarization week the 1-RM test was performed. In the subsequent weeks, the participants arrived at the Exercise Physiology and Biochemistry Laboratory, between 8 a.m. and 10 a.m. and remained at rest seated for a period of 15 min being monitored for HR (Polar™ RS-800, Finland), before the start of each experimental protocol. After this resting period, their BP was measured, and resting blood samples were collected. Then, the participants performed the exercise protocol according to a random order previously established by an independent researcher, and blood samples were collected immediately after the end of each exercise protocol and at 15 and 30 min of recovery (Fig. 1). The professionals who performed the blood sample analyzes were blinded to the intervention protocols. A washout period of 6–7 days was observed between each trial.

### 2.3. Maximum dynamic strength assessment

To assess muscle strength, a maximum repetition test (1-RM) was performed for the squat exercise on the smith machine, as recommended by the American Society of Exercises Physiologists.[31] The mean values of strength for 1-RM were 58.6 ± 8.8 kg.

### 2.4. Blood samples collection and analysis

Blood samples were collected by antecubital vein puncture, using vacutainer tubes sterilized with separating gel. Blood samples were collected in three 4 mL tubes at rest, immediately after exercise, and at 15 and 30 min of recovery. Immediately after collection, samples were centrifuged (12 min at 3,200 RPM) and plasma was immediately frozen at −20 °C. PTH and BSAP concentrations were determined by the chemiluminescence method (Beckman Coulter™, USA, models DXI 800 and AU680, respectively) within a maximum period of 24 h after collection. All blood sample collections were performed after an overnight fast of 10–12 h.

### 2.5. Blood flow restriction protocol

Blood flow restriction protocol was performed using a pneumatic tourniquet (Missouri™, 9.5 × 90 cm, São Paulo, Brazil) placed in the proximal region of the thigh, at a height equivalent to the gluteal line. The following two BFR protocols associated with RE were used: a) Low BFR pressure: occlusion pressure corresponding to 70% of the systolic blood pressure and b) High BFR pressure: occlusion pressure corresponding to 130% of the systolic blood pressure. Occlusion pressures were maintained during the entire exercise period, including the recovery intervals between series.

### 2.6. Exercise protocol

The protocol consisted of squat exercises on the smith machine. Three sets of 15 repetitions were performed with an interval of 45 s between them. Exercise intensity corresponded to 30% of 1-RM and was performed using a guided squat apparatus (PHYSICUS™, Brazil). Each volunteer performed three protocols, which consisted of the squat exercise on the smith machine with or without blood flow restriction: Resistance exercise without blood flow restriction (RE), resistance exercise with blood flow restriction and low occlusion pressure (RE + BFR70), and resistance exercise with blood flow restriction and high occlusion pressure (RE + BFR130).

Some precautions were taken to minimize the external influence on the studied variables. None of the volunteers performed systematic physical exercise in the three months prior to data

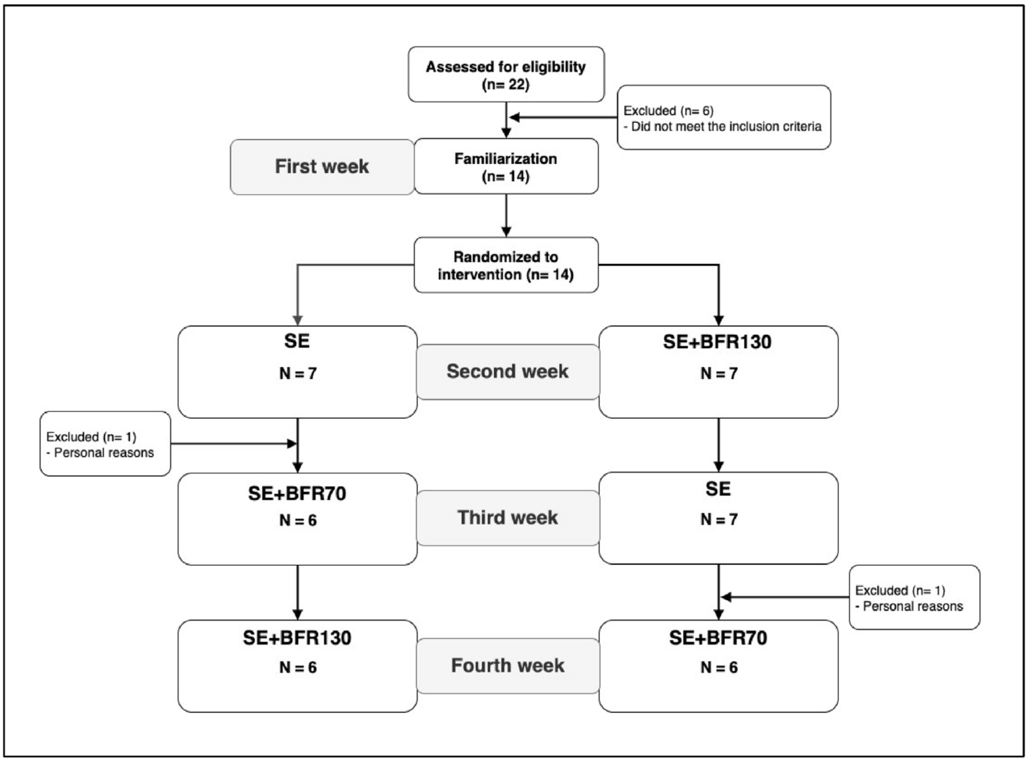


**Fig. 1.** Study design. RE: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1-RM; RE + BFR70: Squatting exercise using a guided bar, performed with a load equivalent to 30% of RM and occlusion pressure corresponding to 70% of the systolic blood pressure; RE + BFR130: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1RM and occlusion pressure corresponding to 130% of systolic blood pressure.

collection. To minimize the effects of diet on calcium concentrations, all participants were instructed to maintain regular nutrition throughout the data collection period. Throughout the experiment, all participants were asked about any dietary changes. No changes were identified in the consumption of the main sources of calcium (e.g., milk and dairy products, soy, green leaves and seeds such as sesame, linseed, among others).

### *2.7. Ethical aspects*

Each volunteer was properly informed about objectives and procedures of the research, and signed a consent form, agreeing to participate in the study, which was approved by the Research Ethics Committee Involving Humans (Protocol number: 1.309.612).

### *2.8. Statistical analysis*

Normality, homoscedasticity, and sphericity were assessed using the Shapiro-Wilk, Levene and Mauchly tests, respectively. When the data normality assumption was not satisfied, logarithmic adjustments and Greenhouse-Geisser correction were performed. Descriptive statistics were used, with all variables expressed as means and standard deviations. Comparisons between collection time points (at rest, immediate post-training, and at 15 min and 30 min of recovery) and between groups (RE, RE + BFR70, and RE + BFR130) were performed using analysis of variance for repeated measures (ANOVA 4 × 3), with SIDAK test for multiple comparisons. All tests were two-tailed, and the significance level was set at 5%.

Effect sizes for the PTH and BSAP variables were calculated as suggested by Cohen.[32] Effect sizes were classified, according to Sawilowsky,[33] as very small (<0.19), small (0.20–0.49), medium (0.50–0.79), large (0.80–1.19), very large (1.20–1.99), and huge (>2.0).

## 3. Results

The acute responses of PTH concentrations to the RE, RE + BFR70 and RE + BFR130 protocols are shown in Table 1. The PTH values at 15 min of recovery were significantly higher than rest and post-exercise only in protocols with blood flow restriction ($p < .05$). Regardless of BFR, PTH concentrations significantly decreased ($p > .05$) from rest to the period immediately after exercise in all experimental protocols. At 30 min of recovery, all PTH values were significantly higher ($p > .05$) than at 15 min of recovery.

**Table 1**
Parathyroid hormone (PTH) plasma concentrations measured at rest, immediately after squat exercise using a guided bar, and at 15 and 30 min of recovery. Values are expressed as means and standard deviations (SD).

| | Rest | | Post-exercise | | Rec 15 min | | Rec 30 min | |
|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| RE | 26.25 | 5.86 | 17.17* | 3.83 | 30.83* | 7.43 | 24.83@ | 6.03 |
| RE + BFR70 | 23.92 | 8.63 | 14.17* | 5.41 | 31.92*# | 12.39 | 21.58@ | 8.47 |
| RE + BFR130 | 25.42 | 8.03 | 16.08* | 6.37 | 38.5*# | 13.62 | 26.08@ | 7.03 |

RE: Resistance Exercise (Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1-RM; RE + BFR70: Squatting exercise using a guided bar, performed with a load equivalent to 30% of RM and occlusion pressure corresponding to 70% of the systolic blood pressure; RE + BFR130: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1RM and occlusion pressure corresponding to 130% of systolic blood pressure. *Statistically significant difference from the previous measure for all evaluated groups ($p < .05$). #Statistically significant difference in relation to rest and post-exercise for interventions with blood flow restriction (RE + BF70, RE + BFR130) ($p < .05$). @Statistically significant difference between post-training and 15 min of recovery ($p < .05$).

There were no significant differences in BSAP concentrations ($p$ >.05) between the different time points (at rest, immediate post-exercise, and 15 and 30 min of recovery) or between RE, RE + BFR70, and RE + BFR130 groups (Table 2).

The effect sizes for the PTH and BSAP variables are shown in Fig. 2. The effect size for the PTH was calculated considering the measures at rest and 15 min of recovery (post-exercise), and for the BSAP the effect size was calculated considering the rest and recovery measures (post-exercise).

Effect sizes for PTH were classified as: medium for RE (ES = 0.78; IC95% = −0.50 to 1.58), large for RE + BFR70 (ES = 0.93; IC95% = 0.08 to 1.73) and very large for RE + BFR130 (ES = 1.63; 95% CI = 0.71 to 2.45). For BSAP, the effect sizes were classified as very small for RE and RE + BFR70 and small for RE + BFR130 (ES = 0.05; IC95% = −0.75 to 0.83, ES = 0.02; IC95% = −0.78 to 0.85 and ES = −0.20; 95%CI = −1.00 to 0.65, respectively).

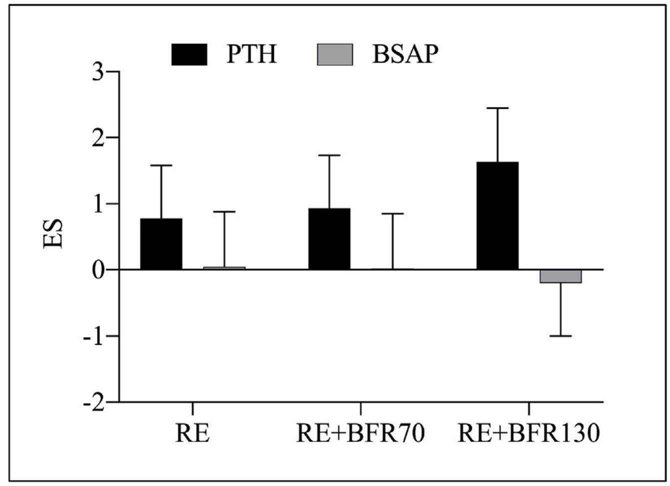


**Fig. 2.** Effect size and respective confidence intervals (95%CI) for parathyroid hormone (PTH) and bone-specific alkaline phosphatase (BSAP) variables. The effect size for PTH was calculated considering the measurements at rest and 15 min post-exercise, and for the BSAP the effect size was calculated considering the measurements at rest and 30 min post-exercise.

## 4. Discussion

The main finding of the present study was the fact that a single resistance exercise performed with BFR was effective in promoting a peak in PTH concentrations 15 min after the end of the exercise, and that these values returned to the pre-exercise values at 30 min of recovery.

Currently, few studies found in the literature analyzed bone metabolism and the practice of physical exercise with blood flow restriction, in addition, these studies analyzed a variety of intervention protocols (different types of exercises, volumes and intensities) and used different biomarkers,[29] a condition that substantially hinders more direct comparisons between the results found.

In the literature we had access to, we did not find any study that analyzed acute PTH responses to resistance exercise associated with blood flow restriction. In other types of protocol, such as the one evaluated by Hamano et al.,[34] who used high and low intensity intermittent aerobic exercises on a cycle ergometer, PTH concentrations were not altered in response to exercise. In this sense, it is worth highlighting the importance of new studies comparing resistance and aerobic exercises associated with blood flow restriction, with a view to understanding whether the PTH behavior is dependent on the type of exercise.

Independently of vascular occlusion, RE led to an acute decrease in PTH levels immediately after exercise and to an increase in PTH levels at 15 min of recovery. However, PTH values were higher than those at rest only in BFR protocols (RE + BFR70 and RE + BFR130). Hock and Gera[6] showed that intermittent peaks of PTH favor the stimulation of bone formation and, consequently, the increase in bone mass. Neer et al.[3] corroborated this result by reporting the beneficial effects of daily administration of PTH on bone mass increase and fracture prevention in post-menopausal women with osteoporosis. In this sense, our findings support the indication of resistance exercise, especially associated with blood flow restriction, as an important non-pharmacological alternative for bone health, since the PTH kinetics after exercise, demonstrated in the present study, were similar that of exogenous hormone administration protocols, a condition that has positive effects on bone metabolism.

**Table 2**
Bone-specific alkaline phosphatase (BSAP) plasma concentrations measured at rest and at 30 min of recovery after squat exercise using a guided bar. Values are expressed as means and standard deviations (SD).

| | Rest | | Rec 30 min | |
|---|---|---|---|---|
| | Mean | SD | Mean | SD |
| RE | 12.20 | 4.01 | 12.39 | 4.03 |
| RE + BFR70 | 12.80 | 4.26 | 12.87 | 4.65 |
| RE + BFR130 | 11.41 | 3.61 | 10.68 | 3.71 |

RE: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1-RM; RE + BFR70: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1RM and occlusion pressure corresponding to 70% of the systolic blood pressure; RE + BFR130: Squatting exercise using a guided bar, performed with a load equivalent to 30% of 1RM and occlusion pressure corresponding to 130% of systolic blood pressure.

The mechanisms involved in PTH concentration regulation include biochemical signals, such as calcium (Ca) and blood pH,[35] and stimulation mediated by the sympathetic nervous system.[36,37] Although the present study did not evaluate metabolic acidosis, the study developed by Lopez et al.[35] provides evidence to help understand the behavior of PTH levels obtained in our study. These authors demonstrated that an increase in metabolic acidosis in dogs induced by an EDTA infusion led to increased PTH plasma concentrations. This mechanism may be associated with the increase in PTH levels after exercise (at 15 min of recovery) that was observed in our study, when the values of PTH were higher than those at rest in BFR groups. Hence, the fact that PTH levels were higher than those at rest only in BFR protocols (RE + BFR70 and RE + BFR130) may be associated with a more marked acidosis in these vascular occlusion protocols, already shown in other studies that used this technique.[36,37]

Rong et al.,[38] studying the effects of exercise on hormonal regulation, found that the reduction in blood pH, resulting from physical exercise, is directly linked to the increase in plasma PTH levels, since the decrease in pH evidenced by increases in hydrogen ion concentrations, reduces calcium concentrations, which is the main signal for PTH regulation. One of the characteristics of the experimental protocols of the present study was the use of the BFR exercise. As demonstrated in the literature, the restriction of blood flow implies a selective reduction in blood efflux from the muscle, causing an accumulation of blood with low partial pressure of oxygen in the capillaries, which significantly increases the production of protons and lactic acid,[39,40] condition that increases metabolic acidosis.[41]

The findings by Lopez et al.[35] regarding the relationship between metabolic acidosis and PTH suggest that the increase in metabolic acidosis caused by strength exercise combined with BFR may explain PTH behavior 15 min after training, especially when exercise is combined with BFR.[39,40]

BSAP was another bone metabolism marker analyzed in the present study. There were no significant alterations in BSAP concentrations between the assessed experimental protocols. Considering that studies involving acute BSAP responses to a single strength exercise with BFR are still scarce in the literature, we postulate that exercises using higher occlusion pressures, such as those presented in the present study (130% of systolic blood pressure), could enhance BSAP acute response to exercise, a fact not supported by our findings.

Bemben et al.[24] did not find changes in BSAP plasma levels immediately after exercise training, neither at 30 min of recovery from a knee extension exercise performed with BFR (20% of 1-RM). On the other hand, BSAP concentration increases when several exercises are used in a single training session,[41] or in chronic intervention protocols were used.[24,42,43]

Considering the studies mentioned above, it appears that acute BSAP responses are related to exercise volume, since acute increases in BSAP concentrations were observed after training sessions involving various exercises. In this sense, even using high occlusion pressure, the protocol used in the present study was not able to promote important acute changes in BSAP concentrations. Perhaps the use of several exercises with BFR in the same session of RE can be effective to promote changes in the concentrations of BSAP, creating an acute metabolic condition favorable to bone metabolism.

## 5. Conclusion

In conclusion, our results showed that protocols involving a single resistance exercise with blood flow restriction using occlusion pressures equivalent to 70% and 130% of systolic blood pressure were efficient in promoting peak PTH concentrations at 15 min post-exertion. This condition produced by exercise with BFR promotes a metabolic condition that may be favorable to bone metabolism.

## Authorship statement

**Category 1**.

Conception and design of study: DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; DA SILVA- GRIGOLETTO, M.E.

Acquisition of data: DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; COPATTI, A.C.; BONORINO, S.L.; SARETTO, C.B.; GROSSL, F.S.; DA SILVA-GRIGOLETTO, M.E.

Analysis and/or interpretation of data: DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; BONORINO, S.L.; DA SILVA-GRIGOLETTO, M.E.

**Category 2**.

Drafting the manuscript: DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; COPATTI, A.C.; BONORINO, S.L.; SARETTO, C.B.; GROSSL, F.S.; DA SILVA-GRIGOLETTO, M.E.

Revising the manuscript critically for important intellectual content: DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; COPATTI, A.C.; BONORINO, S.L.; SARETTO, C.B.; GROSSL, F.S.; DA SILVA-GRIGOLETTO, M.E.

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Approval of the version of the manuscript to be published (the names of all authors must be listed): DE SÁ. C.A.; COPATTI, S.L.; CORRALO, V.S.; COPATTI, A.C.; BONORINO, S.L.; SARETTO, C.B.; GROSSL, F.S.; DA SILVA-GRIGOLETTO, M.E.

## Study limitations

A limitation of the present study was the use of occlusion pressures relative to systolic blood pressure (70 and 130% of systolic blood pressure).

Dietary sodium intake was not controlled; however, participants were instructed to maintain a regular diet and were monitored throughout the study. No changes were identified in the consumption of the main sources of calcium (for example, milk and dairy products, soy, green leaves and seeds such as sesame, linseed, among others).

## Declaration of competing interest

There is no conflict of interests.


## Acknowledge

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