

## High-intensity interval training versus moderate-intensity continuous training on cardiac autonomic control in hypertensive patients

### Treinamento intervalado de alta intensidade versus treinamento contínuo de moderada intensidade no controle autonômico cardíaco de pacientes hipertensos

Fabrício Olinda de Souza Mesquita<sup>1</sup> , Victor Ribeiro Neves<sup>1</sup> , Eduardo Seiji Numata Filho<sup>1</sup> , Sérgio Rodrigues Moreira<sup>2</sup> , Aparecida Maria Catai<sup>3</sup> , Paulo Adriano Schwingel<sup>1</sup> .

1. Universidade de Pernambuco (UPE), Petrolina, PE, Brazil

2. Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina, PE, Brazil

3. Universidade Federal de São Carlos (UFSCAR), São Carlos, SP, Brazil

#### ABSTRACT

**Aim:** This study aims to verify and compare the acute and chronic effects of high-intensity interval training and moderate-intensity continuous training sessions on the linear and nonlinear heart rate variability indexes, responses of blood pressure, aerobic power, aerobic capacity, and quality of life from patients with systemic arterial hypertension. **Methods:** Controlled, randomized clinical trial with intention-to-treat analysis. Non-alcoholic, non-diabetic patients between 18 and 60 years of age, with a diagnosis of prehypertension or stage I hypertension for at least 12 months and with controlled blood pressure levels. **Conclusion:** This protocol study intends to show that high-intensity interval exercise in controlled hypertensive patients with low cardiovascular risk has a greater hypotensive effect, as well as an increase in vagal modulation on the heart.

**Keywords:** hypertension; high-intensity interval training; blood pressure monitoring, ambulatory; cardiorespiratory fitness.

#### RESUMO

**Objetivo:** O presente estudo tem como objetivo verificar e comparar os efeitos agudos e crônicos do treinamento intervalado de alta intensidade e do treinamento contínuo de moderada intensidade sobre os índices lineares e não lineares de variabilidade da frequência cardíaca, respostas da pressão arterial, potência aeróbia, capacidade aeróbia e qualidade de vida de pacientes com hipertensão arterial sistêmica. **Métodos:** Ensaio clínico randomizado e controlado com análise por intenção de tratar. Pacientes entre 18 e 60 anos, não etilistas e não diabéticos, com diagnóstico de pré-hipertensão ou hipertensão estágio I há pelo menos 12 meses, com níveis pressóricos controlados. **Conclusão:** Este protocolo de estudo pretende demonstrar que o exercício intervalado de alta intensidade em hipertensos controlados, com baixo risco cardiovascular, tem um maior efeito hipotensor, bem como aumenta a modulação vagal no coração.

**Palavras-chave:** hipertensão; treinamento intervalado de alta intensidade; monitorização ambulatorial da pressão arterial; aptidão cardiorrespiratória.

Received: July 23, 2021; Accepted: November 22, 2021.

Correspondence: Fabrício Olinda de Souza Mesquita, Av. José de Sá Maniçoba, s/n - Centro, 56304-205 Petrolina PE, fabricio.souza@ebserh.gov.br

## Introduction

Several studies have focused on comparing the effects of high-intensity interval training (HIIT) versus moderate-intensity continuous training (MICT) in hypertensive populations. Two elegant systematic reviews with meta-analyses [1,2] have not observed a superior effect of HIIT to MICT in systolic and diastolic blood pressures reduction. On the other hand, HIIT favored an improvement in aerobic fitness with the greatest increase in  $VO_{2max}$  [1,2].

It is well established in the literature that just one aerobic exercise session can reduce blood pressure recovery when compared to pre-intervention moments. In addition, aerobic exercise promotes beneficial adaptations in other health variables, such as aerobic fitness [3, 4]. This acute response is positively related to the chronic effect of aerobic training in blood pressure [2,5]. However, this association has only been clinically observed, which emphasizes the need for investigating outpatient blood pressure levels [6], which may have minimized the effects of the observer (white coat syndrome) and better reflect the actual blood pressure values in daily activities [7].

If, on the one hand, the risk for fatal and non-fatal cardiovascular events may increase due to the increase in exercise intensity [8,9], on the other hand, the safety and risk-benefit of prescribing HIIT in individuals with impairment chronic cardiac failure have already been demonstrated by the decrease in premature ventricular contractions and increase in vagal tone after a session of high-intensity interval exercise [10]. Previous studies on the effects of HIIT on the autonomic nervous system in hypertensive patients remain scarce in the literature. Since autonomic dysfunction has been demonstrated in this population, it is speculated that both HIIT and MICT may improve cardiac autonomic control and as such treat systemic arterial hypertension (SAH) and its progression [8].

Besides, HIIT promoted an increase in vagal tone after a session of high-intensity interval exercise [10] and decrease arrhythmic events in a 24-h post-training period in heart failure patients. In addition, studies involving hypertensive patients have not reported adverse events during HIIT programs [2]. However, further investigations are still needed to assess the autonomic control and potential cardiac arrhythmias after a session of intense aerobic exercise in hypertensives.

Therefore, the main purpose of this study is to assess and compare the effects of HIIT and MICT on the cardiac autonomic nervous system in patients with hypertension. Additionally, the secondary aims are 1) to assess HIIT effects on blood pressure, aerobic capacity, aerobic power, and quality of life; 2) to assess acute responses of HIIT on heart rate variability after one exercise session; 3) to identify potential adverse cardiovascular effects of HIIT in patients with hypertension.

## Methods

### *Study design*

This is a controlled, randomized clinical trial with intention-to-treat analysis [11] that will be carried out at the Exercise Physiology Laboratory, located in the Department of Physical Education (CEFIS) of the *Universidade Federal do Vale do São Francisco* (UNIVASF) and in the Human Performance Research Laboratory at *Petrolina Campus of the Universidade de Pernambuco* (UPE).

This study was approved by the Brazilian Clinical Trials Records (REBEC) [Clinicaltrials.gov, REBEC registration: RBR-2fdkw3] and the Research Ethics Committee (CEP) from UPE (CAAE registration: 69902817.5.0000.5207) and conducted according to the principles outlined in the Declaration of Helsinki. Only participants who provide written informed consent will be enrolled in the study.

### *Sample selection*

The volunteers will be referred to a cardiological evaluation, which includes a cardiac stress test on a treadmill and lipid blood test panel plus fasting glucose. In sequence, an anamnesis will be performed by a researcher to obtain personal information, alcohol intake behavior, drug use, tobacco use behavior, and physical activity. Height, body weight, frequency of daily administration of blood pressure-lowering drugs, and other medicines will be recorded. Current alcohol use will be assessed as the frequency of alcohol consumption and the amount of alcohol consumed per drinking day. The frequency (in days) and duration (in minutes) of physical activities will be self-reported.

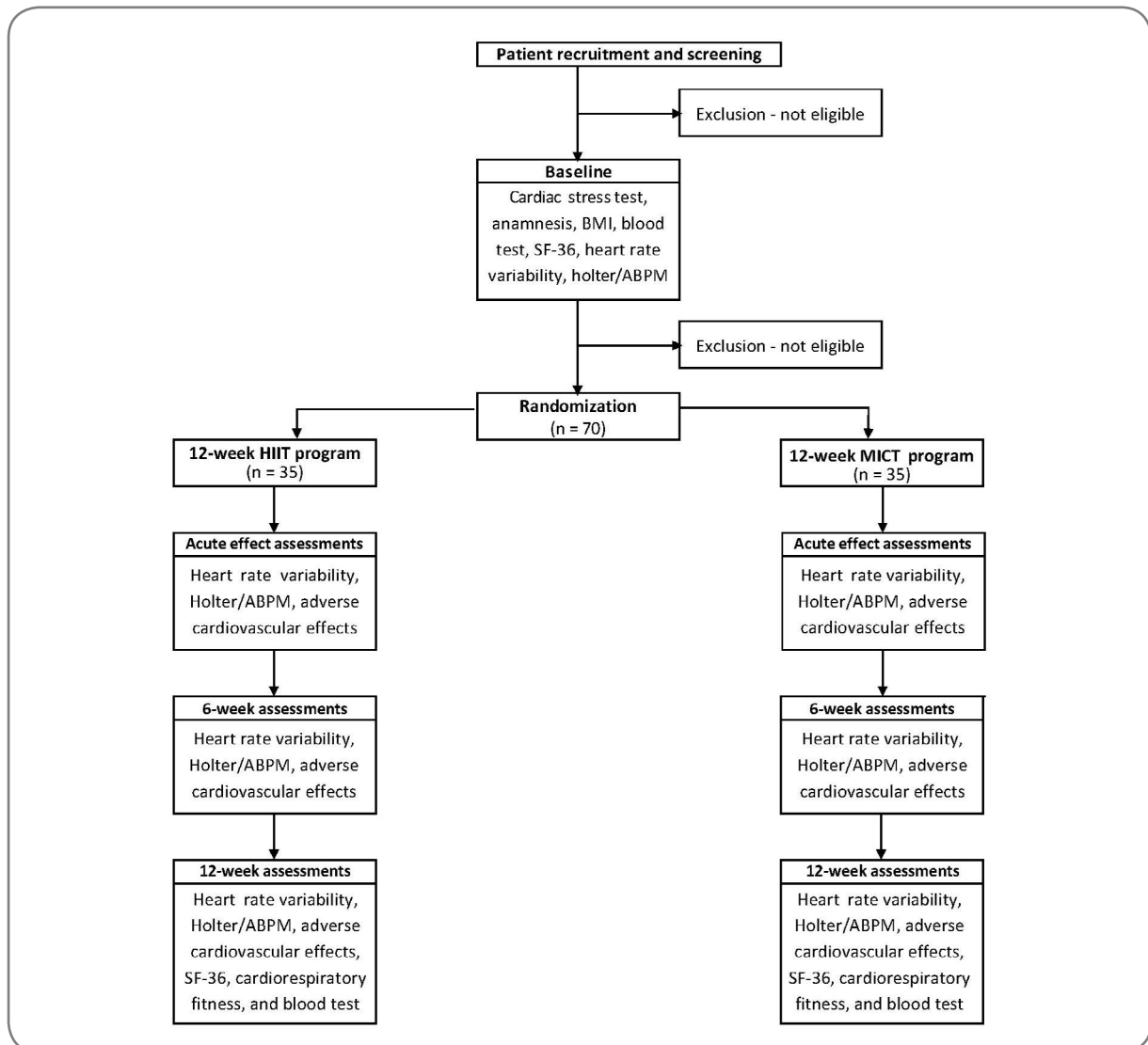
It will not be included patients with secondary hypertension, ischemic heart disease, heart failure, complex arrhythmias, tachyarrhythmia, and/or atrial fibrillation diagnosed by a cardiologist during the exercise stress test. Will also not be included volunteers with body mass index (BMI)  $\geq 35$  kg.m<sup>-2</sup>, who regularly practiced physical activity at least one day per week during the previous three months (sedentary lifestyle), frequent drinkers (a history of ethanol intake  $> 20$  g/day or  $> 140$  g/week), pregnant women, and/or diabetics (fasting blood glucose level of 126 mg/dL or higher).

The inclusion criteria adopted will be adults from 18 to 60 years old with a diagnosis of prehypertension or stage 1 hypertension for at least 12 months with blood pressure levels controlled by antihypertensive drugs with no changes in the medication dosage in the previous three months.

It will be excluded those who present any osteoarticular, cardiovascular, and/or metabolic changes that prevented them from continuing in the study or the patients who change the medication.

Hereafter, volunteers will proceed to the pre-intervention evaluations: 1) HRV in the supine and orthostatic positions (20 minutes), and the 24-hour using a Holter electrocardiogram; 2) ambulatory blood pressure monitoring for 24 hours; 3) aerobic

capacity and aerobic power through the incremental test (TI); 4) quality of life by the SF-36 questionnaire. It should be noted that all assessments will be standardized to take place in the morning. Likewise, the evaluation schedule for everyone will be maintained throughout the study (Figure 1).



HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; BMI = body mass index; ABPM = ambulatory blood pressure monitoring; SF-36 = Medical Outcomes Study 36 – Item Short-Form Health Survey

**Figure 1** - Schedule of enrolment, interventions, and assessments

Sample randomization will be undertaken at the end of pre-intervention evaluations through a hidden sequence of blocks randomly exchanged and stratified by sex, generated by an independent researcher using the random numbers from Excel® (Microsoft Corporation, Redmond, WA, United States of America [USA]). The study will be conducted by researchers who will be blinded to: 1) conducting evaluations of outcome measures, and 2) carrying out statistical procedures. In addition, all participants will be instructed not to disclose which of the groups they have been allocated.

### *Outcome measures*

The primary outcome of the trial is to assess and compare the effects of 12-week HIIT intervention on the cardiac autonomic control by heart rate variability indexes in individuals with prehypertension or with stage 1 hypertension. Secondary outcomes are changes in cardiorespiratory fitness, blood pressure levels, maximal capacity power, and adverse cardiovascular effects.

### **Procedures**

#### *Heart rate variability indexes*

Before this assessment, patients will be instructed not to consume alcoholic and/or caffeinated beverages 24 hours before assessments. In addition, all volunteers will have to present respiratory rates within the range of the high frequency band (HF: from 0.15 to 0.40 Hz), that is, greater than 9 breaths per minute.

The patients will remain at rest for 10 minutes. After that, R-R intervals (RRi) will be recorded for 10 minutes in the supine position and 10 minutes in the orthostatic position. At this time, RRi are recording by Wincardio electrocardiogram recorder (MICROMED Biotecnologia Ltda., Brasilia, DF, Brazil) with 12 simultaneous leads placed on the patient's chest at specific points to a receiver and then to the computer for further analysis.

HRV analysis in the frequency domain (spectral analysis) will be performed using an autoregressive model [12], and the low-frequency (LF: from 0.04 to 0.15 Hz) and HF (from 0.15 to 0.40 Hz) bands will be obtained. The sequence of RRi with 256 beats and with the greatest stability will be selected for each subject. This sequence will be used for both linear and nonlinear analysis. In addition, the mean and variance of the RRi will also be calculated according to the Catai checklist [13].

The normalization of the indices will consist of dividing a given power of each spectral component (LFabs or HFabs) by the total power minus the very low frequency (VLF: < 0.04 Hz), and then multiplying the ratio by 100 [14,15]. These spectral components will be expressed in absolute units (LFabs and HFabs) and normalized units (LFun and HFun) [16].

For nonlinear analysis, the RRi will be transformed into a sequence of symbols (numbers) ranging from 0 to 5. Then, the patterns of a sequence of 3 beats will be determined. The pattern distribution will be calculated using Shannon's entropy (SE). This index describes the distribution of patterns. SE is high if the distribution is flat (all patterns are identically distributed, and the series carries as much information as possible). On the other hand, SE is low if a subset of patterns is more common, while other patterns are absent or infrequent [15, 16].

To perform symbolic analysis (SA), all patterns will be grouped into four families as follows: (a) patterns without variation (0V: all symbols are equal, i.e. 2,2,2 or 4,4,4); (b) patterns with one variation (1V: 2 consecutive symbols are the same and one symbol is different, i.e. 4.2.2 or 4.4.3); (c) patterns with two similar variations

(2LV: 3 symbols that form an ascending or descending ramp, i.e. 5.4.2 or 1.3.4); (d) two different variations (2ULV: 3 symbols that form a peak or a tail, i.e. 4,1,2 or 3,5,3). The rate of occurrence of each pattern is defined as 0V%, 1V%, 2LV%, and 2ULV%, and 0V% and 2ULV% may be considered markers of sympathetic and vagal modulation, respectively.

Furthermore, the conditional entropy (CE) will also be assessed through the complexity index (CI). This index will be normalized by the SE of the RRI series to obtain a normalized CI (NCI), thus expressing the complexity in terms of dimensional units, ranging from 0 (null information) to 1 (maximal information). The higher the CI and the NCI, the greater the complexity and the less regular the series [16].

### *Twenty-four-hour ambulatory blood pressure monitoring and Holter monitoring*

The simultaneously 24-hour ambulatory blood pressure monitoring (ABPM) and 24-hour Holter monitoring will be performed using the oscillometric device CardioMapa (CARDIOS, São Paulo, SP, Brazil). Measurements will be taken every 20 minutes during the waking period (6 am to 11 pm), and every 30 minutes during the sleep period (11 pm to 6 am). The time between bedtime and getting up will be considered as a sleep period, which will be noted down in the diary of each volunteer.

After automatic scanning, an expert analyst carefully will edit all the recordings. Annotated RRI time series will be finally transferred to a personal computer and will process according to previously described criteria [14] to identify ectopic beats, arrhythmic events, and artifacts [17,18].

### *Cardiopulmonary exercise testing*

An incremental protocol [19] on a mechanically braked cycle ergometer Biotec 2100 (CEFISE®, São Paulo, SP, Brazil) will be used for the cardiopulmonary exercise testing (CPET). All individuals will be instructed not to consume stimulating and/or alcoholic beverages on the day before the test. CPET will start with a load of 30 Watts and the cadence was maintained at  $60 \pm 5$  revolutions per minute (rpm). There will be increments of 15 Watts of load at each stage, lasting 2 minutes, until the maximum voluntary exhaustion of the subject [19]. The final stage will be defined by the completion of at least 51% of the total time.

Pulmonary ventilation, oxygen consumption, and heart rate will be monitored and recorded continuously using an ergospirometer Fitmate Pro (COSMED Srl, Rome, Italy). Peak oxygen consumption will be defined as the highest value reached in the final 20 seconds of the test.

### *Quality of life assessment*

The Brazilian version of the validated SF-36 quality of life questionnaire [20] will be administered. The questionnaire is a generic multidimensional 36-item instrument for assessing the quality of life, encompassing eight dimensions or components: functional capacity, physical aspects, pain, general health status, vitality,

social aspects, emotional aspects, and mental health. The questionnaire score ranges from 0 to 100, in which 0 corresponds to the worst general health status and 100 to the best health status [20].

### Sample size

Given the pragmatic nature of the trial, a reduction of 3.2 mmHg in systolic blood pressure in the HIIT group compared to the MICT group is considered a clinically relevant difference according to a systematic review with meta-analysis of studies on the effects of endurance training, resistance training, and combined training in the ambulatory blood pressure [21]. In the present study, a sample size of 35 patients in each group will be sufficient to detect this difference according to the G\*Power software (Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany) assuming a standard deviation of 3.8 mmHg, a power of 80%, and a significance level of 5%. The assumed standard deviation is based on observations from Cornelissen and Smart [21].

### Experimental intervention – training protocol

Training with their respective exercise sessions will be carried out in a controlled temperature environment ( $22 \pm 1^\circ\text{C}$ ), with a relative humidity of  $55 \pm 5\%$ . In both training groups, the exercise sessions will be performed on the same mechanically braked cycle ergometer Biotec 2100 (CEFISE®) twice a week, for 12 weeks. Additionally, a cadence of  $60 \pm 5$  rpm will be maintained for both training protocols.

HIIT sessions will start with a five-minute warm-up with no load. During the entire study period, 10 one-minute series will be performed at 80 to 90% of maximum power output (Pmax), with a two-minute interval between the series at 40% of Pmax. All sessions in the different phases of the training will last 30 minutes.

Likewise, MICT sessions will start with a five-minute warm-up without load. The load used will be adjusted to 50% of the Pmax during the entire training period. Exercise volumes of HIIT and MICT will be equalized according to Buchheit and Laurssen [22]. Table I shows the training periodization.

**Table I** - Periodization of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) individuals with essential arterial hypertension classified as borderline or stage I

| Weeks                            | HIIT     |           |            |               | MICT     |           |            |               |
|----------------------------------|----------|-----------|------------|---------------|----------|-----------|------------|---------------|
|                                  | Load (%) | Serie (n) | Time (min) | Volume (a.u.) | Load (%) | Serie (n) | Time (min) | Volume (a.u.) |
| 1 <sup>a</sup> a 4 <sup>a</sup>  | 80%      | 10X       | 1 min      | 1.600 a.u.    | 50%      | 1X        | 32 min     | 1.600 a.u.    |
|                                  | 40%      | 10X       | 2 min      |               |          |           |            |               |
| 5 <sup>a</sup> a 8 <sup>a</sup>  | 85%      | 10X       | 1 min      | 1.650 a.u.    | 50%      | 1X        | 33 min     | 1.650 a.u.    |
|                                  | 40%      | 10X       | 2 min      |               |          |           |            |               |
| 9 <sup>a</sup> a 12 <sup>a</sup> | 85%      | 10X       | 1 min      | 1.700 a.u.    | 50%      | 1X        | 34 min     | 1.700 a.u.    |
|                                  | 40%      | 10X       | 2 min      |               |          |           |            |               |

The training volume was calculated using the equation: volume = loads X series X times [33]; a.u.: arbitrary unit

### Statistical analysis

The data will be double entered into the SPSS software (SPSS Inc., Chicago, IL, USA) with an automatic amplitude and consistency checking. All statistical analysis will be carried out in the SPSS by a blinded statistician. The statistical analysis will be descriptive with the Shapiro–Wilk assessing the normality of the data. Categorical variables will be described in absolute and relative frequencies (number and percentages) and the continuous variables as mean  $\pm$  standard deviation in a parametric distribution or as median (first quartile – third quartile) in case of non-Gaussian distribution. The homogeneity of the data will be verified by Levene’s test.

The primary endpoint for the statistical analysis is the mean change in heart rate variability indexes from baseline to 12 weeks of follow-up. The primary endpoint will be compared between intervention arms using a general linear model with the treatment group, baseline HRV, and 6-week HRV fitted as covariates, and 12-week HRV as the dependent variable. The linear model will be adjusted for the continuous covariate age and the categorical covariate sex. Further adjustment variables may be investigated as part of the exploratory analysis.

The secondary endpoints will be analyzed using the same covariates as the primary endpoint analysis. Likewise, the differences between groups in terms of continuous secondary outcome measures will be assessed with the same statistical model as the primary outcome analysis. Differences between treatment arms for binary, unordered categorical and ordinal secondary outcome variables will be analyzed using logistic regression, multinomial logistic regression, and proportional odds models, respectively.

The primary and secondary endpoints analyses will be two-tailed with the alpha level set at 5%. Effect sizes, 95% confidence intervals, and statistically and clinically significant differences will be calculated. All secondary analyses will be exploratory if a non-significant result is obtained from the primary analysis and, whenever reported, the failure to achieve a significant result in the primary analysis will be declared. All analyses will be performed on an intention-to-treat basis.

All data will be summarized and reported following the Consolidated Standards of Reporting Trials (CONSORT) guideline. No formal interim analyses are anticipated.

## Discussion and expected results

This protocol study intends to show that high-intensity interval exercise in controlled hypertensive patients with low cardiovascular risk, has a greater hypotensive effect, as well as an increase in vagal modulation on the heart. In addition, it is expected that the degree of blood pressure reduction, right after an acute exercise session, is related to the magnitude of the blood pressure change, especially after the application of high-intensity interval training.



In addition, the basis of these results, other studies may be carried out in different clinical conditions and training modalities, to provide health professionals with information that identifies the degree of safety in performing aerobic exercises with a higher degree of intensity and in populations with clinical or pathological limitations, such as arterial hypertension.

Besides that, Pescatello *et al.* [23] recently published a systematic review involving adults with and without hypertension. They included 17 meta-analyses and one systematic review. Of these, six were on the effect of aerobic exercise on blood pressure and reported a significant reduction in systolic and diastolic blood pressure. However, none of the systematic reviews included assessed the effects of HIIT. Moreover, there appears to be no published meta-analysis on the effects of HIIT in hypertensive patients. Furthermore, the meta-analysis technique minimizes subjectivity by standardizing the treatment effects of relevant studies according to effect size, by pooling results, and by analyzing the resulting data [23]. Then more studies are needed on the efficacy and safe of alternative exercise protocols on health in varied clinical situations.

## Dissemination and impact

Throughout the clinical trial, media outlets (including social media) will be informed of progress, and the experiences gained will be presented at national conferences. On completion, the study results will be published in peer-reviewed journals and presented at scientific meetings.

### Potential conflicts of interest

No potential conflicts of interest relevant to this article have been reported.

### Financing source

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001; the Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco (FACEPE) [grant numbers APQ-0246-4.06/14, APQ-0789-4.08/17]; and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) [grant number 426706/2016-1].

### Author's contributions

**Study conception and design:** Mesquita FOS, Neves VR, Catai AM, Schwingel PA; **Draft manuscript preparation:** Mesquita FOS, Neves VR, Numata Filho ES, Catai AM; **Review and editing the manuscript:** Neves VR, Numata Filho ES, Schwingel PA; **Analysis and interpretation of results:** Moreira SR, Schwingel PA; **Critical review and manuscript revision:** Moreira SR, Catai AM; **Project administration:** Neves VR; **Project supervision:** Neves VR, Schwingel PA; **Funding acquisition:** Neves VR, Schwingel PA; All authors reviewed and approved the final version of the manuscript.

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