Functional Capacity of Patients with Pacemaker Due to Isolated Congenital Atrioventricular Block

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Abstract

Background: Isolated congenital atrioventricular block (CAVB) is a rare condition with multiple clinical outcomes. Ventricular remodeling can occur in approximately 10% of the patients after pacemaker (PM) implantation.

Objectives: To assess the functional capacity of children and young adults with isolated CAVB and chronic pacing of the right ventricle (RV) and evaluate its correlation with predictors of ventricular remodeling.

Methods: This cross-sectional study used a cohort of patients with isolated CAVB and RV pacing for over a year. The subjects underwent clinical and echocardiographic evaluation. Functional capacity was assessed using the six-minute walk test. Chi-square test, Fisher’s exact test, and Pearson correlation coefficient were used, considering a significance level of 5%.

Results: A total of 61 individuals were evaluated between March 2010 and December 2013, of which 67.2% were women, aged between 7 and 41 years, who were using PMs for 13.5 ± 6.3 years. The percentage of ventricular pacing was 97.9 ± 4.1%, and the duration of the paced QRS complex was 153.7 ± 19.1 ms. Majority of the subjects (95.1%) were asymptomatic and did not use any medication. The mean distance walked was 546.9 ± 76.2 meters and was strongly correlated with the predicted distance (r = 0.907, p = 0.001) but not with risk factors for ventricular remodeling.

Conclusions: The functional capacity of isolated CAVB patients with chronic RV pacing was satisfactory but did not correlate with risk factors for ventricular remodeling. (Arq Bras Cardiol. 2015; 104(1):67-77)

Keywords: Congenital Heart Diseases; Atrioventricular Block; Child; Artificial Pacemaker; Young Adult; Walk.

Introduction

Atrioventricular (AV) block is a rare congenital condition, with an estimated incidence of 1 case in 20,000 births. Its isolated form, i.e., without associated intracardiac defects, corresponds to approximately 70% of the cases. The pathophysiology of AV block is strongly correlated with maternal autoimmune diseases. The implantation of a permanent pacemaker (PM) is the only form of treatment and results in significant long-term survival rates.

Despite the satisfactory clinical outcome in most cases, approximately 10% of the patients develop severe ventricular dysfunction, even after treatment with a PM. There is evidence that the unfavorable outcome is associated with intrauterine autoimmune myocarditis and with the deleterious effect of chronic pacing of the right ventricle (RV). Considering the rarity of CAVB, the effects of chronic RV pacing on the functional ability remain poorly studied. The data available in the literature were obtained from a small series of cases involving individuals who had not yet undergone PM implantation.

To investigate the functional capacity of children and young adults with PM suffering from CAVB, we conducted a cross-sectional analysis in a prospective cohort comprising individuals with CAVB and artificial cardiac PMs during follow-up in our institution. We hypothesized that chronic RV pacing did not impair the functional capacity of individuals not suffering from structural heart diseases associated with impulse disturbance.

Methods

Study design and population

Between 1982 and 2013, 165 individuals with CAVB underwent a first implantation of a permanent cardiac PM at our institution before completing 21 years of age. This prospective cohort group was monitored for the evaluation of clinical, functional, and echocardiographic effects of chronic cardiac pacing in children and young adults with CAVB (ClinicalTrials.gov ID = NCT01477658).
In the present study, a cross-sectional analysis of this population was performed considering the following inclusion criteria: (1) age < 21 years at the first PM implantation; (2) unifocal RV pacing for > 1 year; (3) absence of intracardiac defects regardless of surgical correction. Subjects with LV or multifocal pacing were not included. The study was approved by the research ethics committee of our institution, and all the subjects signed an informed consent form.

Study outcome

The functional capacity was assessed using the six-minute walk test (6MWT), and the expected outcome was that individuals would walk a distance close to 90% of the predicted value.

Patient recruitment

The subjects were consecutively recruited during outpatient care or by referring to the database of the surgical PM unit.

Analysis of medical records

The medical history of each patient was analyzed with interviews and reviews of medical records. The following data were collected: (1) demographic data; (2) clinical data preceding the PM implantation (during the diagnosis of CAVB), including clinical events, comorbidities, medications used, and electrocardiogram and echocardiogram results; (3) data associated with the first PM implantation (age, time between diagnosis and implantation, type of PM, route of access used, and site of RV pacing).

Population profile at the time of enrollment

At enrollment, all subjects underwent physical examination, Also, a revision of their medical records, including the assessment of heart failure symptoms and use of cardiovascular drugs, was made.

Evaluation of implantable electronic cardiac devices

The evaluation of the cardiac pacing device aimed at determining several parameters, including the pacing mode, atrial pacing, ventricular pacing, heart rate, duration of the QRS complex (spontaneous and with an active PM), mode of operation, and percentage of ventricular pacing. Specific programmers for each PM model and the Hewlett-Packard Page Writer 200 electrocardiograph with capacity for automatic analysis of axes and intervals were used.

Evaluation of functional capacity

The 6MWT was performed according to the guidelines of the American Thoracic Society (ATS). All participants were instructed to walk at the maximum possible speed in a 45-meter long corridor with demarcations on the ground at every meter. Participants were verbally encouraged at two and four minutes after the beginning of the test. The examiner determined the completion of the test after six minutes.

Before beginning and after completing the test, blood pressure, heart rate, and oxygen saturation were measured, and each individual described their level of dyspnea and fatigue using the modified Borg scale. The criteria for test interruption included angina, significant dyspnea, lower limb fatigue, dizziness, profuse sweating, and pallor.

Functional capacity was assessed by evaluating the distance walked during the six minutes (in meters). The predicted distance was calculated using the equation proposed for the Brazilian population.

Electronic data collection and management

Data were stored in a database developed with the Research Electronic Data Capture (REDCap) system, which is hosted on the server of our institution. This software, developed at Vanderbilt University (Tennessee, USA), is fully web-based and enables electronic data collection and management and also study process management, while meeting the criteria set by the international policies on data privacy and security in the health sector. The use of this tool also allowed the validation, auditing, and electronic data export. Figure 1 illustrates the software functionalities.

Variable analysis

Several variables that could influence the functional capacity of the individuals and serve as predictors of ventricular remodeling were studied, including gender, age at first PM implantation, current age, functional class according to the New York Heart Association (NYHA), use of cardiovascular drugs, type of PM in use (ventricular or atrioventricular), length of PM use, duration of artificially stimulated QRS complex, left ventricular ejection fraction (LVEF) using Simpson’s method, left ventricular diastolic diameter (LVDD), left intraventricular electromechanical delay determined by tissue Doppler, and the presence of autoantibodies (anti-Ro/SSA and anti-La/SSB) in the mothers of the study participants.

Statistical analysis

Data were exported to Microsoft Excel spreadsheets and analyzed using SAS (Statistical Analysis System), SPSS (Statistical Package for Social Sciences), and R Studio softwares.

The quantitative variables were described using the mean and standard deviation, and qualitative variables were presented as absolute and relative frequencies.

The correlation of the qualitative variables with the predicted distance achieved in the walk test (greater or smaller than 90%) was measured using chi-square test or Fisher’s exact test. The correlation of the quantitative variables with the predicted distance achieved was analyzed using Pearson’s correlation coefficient. P values ≤0.05 were considered significant.

Results

Between 1982 and 2013, 165 individuals diagnosed with CAVB had undergone the first PM implantation at our institution before completing 21 years of age. Of these, 45 had associated cardiac defects and were not eligible...
for the study. Of the 120 eligible, 61 met the study criteria (Figure 2). Of the remaining subjects, two had died, six had been monitored for other medical complications, and 25 could not be located, and therefore were not considered for follow-up. In addition, 26 other subjects were located but were not included in the study for the following reasons: RV pacing for less than one year or LV pacing at the time of the study in 13 subjects; change to a biventricular type of PM in 4 subjects; cardiac transplantation in one subject; and residing in remote locations in 8 subjects.

Demographic and clinical data were collected during the first PM implantation and are summarized in Table 1. The mean age of participants at the first implantation was 8.5 ± 6.2 years (range 4 days to 20.2 years). The mean period between diagnosis and first PM implantation was 4.8 ± 5.4 years (range from 4 days to 20 years) with a median of 2.5 years.

The clinical events that motivated the PM implantation were symptomatic bradycardia in 44 individuals (72.1%), and included signs and symptoms of heart failure, syncope, presyncope, dizziness, and palpitations. Other patients presented asymptomatic bradycardia with complex ventricular arrhythmia, prolonged QT interval, chronotropic incompetence, or poor weight development.

Preoperative echocardiography was performed in 44 (72.1%) subjects. In all cases, heart in situs solitus, levocardia, and absence of defects in the cardiac septum and valves were observed.

**Data obtained during the first pacemaker implantation**

Unicameral ventricular pacing was used in 65.6% of the implantations, and only three children (4.9%) aged ≤10 years underwent implantation of atioventricular PMs.

The epicardium was used as the access route in 4 of 6 infants and in 5 of 8 pre-school children. The transvenous route through the femoral vein was used as the access route in the remaining groups. The subclavian vein was used as the access route in 43% of the patients comprising pre-school children, school children, and adolescents.

The apical endocardium of RV was the site of pacing in 33 (54.1%) patients. Of the 10 epicardial implants (16.4%), 7 (11.5%) were initially performed in LV.

**Population profile at enrollment**

The profile of the study population at enrollment is summarized in Table 2.
Clinical and pacemaker evaluation

There were no reports of hospitalization for treatment of heart failure from the period of PM implantation until study enrollment. Only three subjects (4.9%) reported symptoms of fatigue during major physical effort. The use of cardiovascular medication was reported by five subjects (8.2%), as shown in Table 2.

The 35 individuals using AV PMs had adequate sinus function, evidenced by a low percentage of atrial pacing (27.0 ± 23.7%, median = 19%). The established limits of minimum frequency of pacing varied between 50 and 80 ppm (59.9 ± 3.1 ppm) and the maximum frequency varied between 110 and 170 ppm (130.7 ± 15.8 ppm).

The 26 individuals with ventricular PMs were using sensors to modulate the pacing frequency. Twenty individuals were using sensors for body movement (accelerometers) and six were using the combination of respiratory minute-volume sensors with body movement. The established limits of minimum frequency of pacing varied between 60 and 80 ppm (70.0 ± 6.3 ppm), and the maximum frequency varied between 120 and 170 ppm (145.7 ± 18.4 ppm).

Evaluation of functional capacity

The 6MWT was performed in 61 subjects, aged between 7 and 41 years. No cases of test interruption or need for special care were reported. The mean walking distance was 546.9 ± 76.2 meters, representing 91.0 ± 12.5% of the value predicted by the equation used in this study (Graph 1). Most participants walked a distance greater than 80% of the predicted value, whereas 18 (29.5%) participants walked distances greater than the values estimated by the equation (Chart 1). Chart 2 shows the strong correlation between the total distance walked and the predicted distance (r = 0.907, p = 0.001).

The cardiorespiratory parameters measured before and after the 6MWT are described in Table 3. All parameters had a normal physiological behavior. However, individuals with responsive ventricular PMs with sensors tended to have a greater variation in heart rate when compared with those treated with AV PMs synchronized with spontaneous P waves (p = 0.141).

Despite the variation detected in the functional capacity, there was no correlation between the distance walked and age, both at the initial PM implantation (r = 0.030,
Table 1 – Demographic and clinical profile of the study group

Baseline demographic and clinical characteristics

| Characteristic                  | Value    |
|--------------------------------|----------|
| Female, N (%)                  | 41 (67.2) |
| Ethnicity, N (%)               |          |
| Caucasian                      | 28 (45.9) |
| Black                          | 3 (4.9)  |
| Mixed                          | 30 (49.2) |
| Time of CAVB diagnosis, N (%)  |          |
| Intrauterine                   | 17 (27.9) |
| Neonatal                       | 8 (13.1)  |
| Infant                         | 12 (19.7) |
| Pre-school age                 | 6 (9.8)   |
| School age                     | 9 (14.8)  |
| Adolescence                    | 9 (14.8)  |
| Time of PM implantation, N (%) |          |
| Neonatal                       | 6 (9.8)   |
| Infant                         | 8 (13.1)  |
| Pre-school age                 | 8 (13.1)  |
| School age                     | 11 (18.0) |
| Adolescence                    | 28 (45.9) |
| Indication for PM implantation, N (%) |        |
| Symptomatic bradycardia        | 44 (72.1) |
| Isolated bradycardia           | 17 (27.9) |
| Comorbidities, N (%)           |          |
| None                           | 58 (95.1) |
| Systemic arterial hypertension | 1 (1.6)   |
| Mitral valve prolapse          | 1 (1.6)   |
| Myocarditis                    | 1 (1.6)   |
| Use of cardiovascular drugs, N (%) |     |
| Not used                       | 57 (93.4) |
| Angiotensin converting enzyme inhibitors | 2 (3.3) |
| Furosemide                     | 1 (1.6)   |
| Beta blockers                  | 1 (1.6)   |
| Heart rate before PM implantation, bpm (mean ± SD) | 51.0 ± 11.9 |
| QRS complex duration before PM implantation (mean ± SD) | 85.5 ± 15.2 |
| Axis of the QRS complex before PM implantation (range) | 30-175 degrees- |
| Ventricular rhythm, N (%)      |          |
| Complete atrioventricular block | 58 (95.2) |
| Mobitz II second-degree atrioventricular block | 1 (1.6) |
| Second-degree atrioventricular block with 2:1 conduction ratio | 2 (3.3) |
| LV ejection fraction (%) - Teicholz (mean ± SD) | 55.6 ± 20.5 |
| End-systolic LV diameter, mm (mean ± SD) | 24.4 ± 9.3 |
| End-diastolic LV diameter, mm (mean ± SD) | 40.0 ± 11.6 |

CAVB: complete congenital atrioventricular block; bpm: beats per minute; SD: standard deviation; LV: left ventricle; PM: pacemaker.

Table 2 – Profile of the study group at the time of enrollment

Profile of the study group

| Characteristic                  | Value    |
|--------------------------------|----------|
| Age at the time of evaluation, years (mean ± SD) | 21.6 ± 8.4 |
| Period of RV stimulation, years (mean ± SD)     | 9.9 ± 5.2  |
| Total length of PM use, years (mean ± SD)       | 13.5 ± 6.3 |

Clinical evaluation

| Cardiovascular drug, N (%) |          |
|----------------------------|----------|
| Atenolol                   | 1 (1.6)  |
| Atenolol and enalapril     | 2 (3.3)  |
| Captopril and aspirin      | 1 (1.6)  |
| Losartan and hydrochlorothiazide | 1 (1.6) |

Evaluation of pacemaker

| Type of PM, N (%) |          |
|-------------------|----------|
| Ventricular       | 26 (42.6) |
| Atrioventricular  | 35 (57.4) |
| Percentage of ventricular pacing, % (mean ± SD) | 97.9 ± 4.1 |
| Duration of stimulated QRS, ms (mean ± SD)       | 153.7 ± 19.1 |
| Duration of inhibited QRS, ms (mean ± SD)         | 88.7 ± 12.6 |
| Heart rate, N (%)                                    |
| Sequential atrioventricular pacing                 | 19 (31.1) |
| Exclusive ventricular pacing (AV dissociation)     | 26 (42.6) |
| Ventricular pacing synchronized to P waves         | 16 (26.6) |
| Site of RV stimulation, N (%)                       |
| Interventricular septum                            | 20 (32.8) |
| Other RV regions (including the apical septum)     | 41 (67.2) |

Echocardiographic study

| Characteristic                  | Value    |
|--------------------------------|----------|
| LV ejection fraction, % (mean ± SD) | 54.7 ± 7.1 |
| Diastolic LV diameter, mm (mean ± SD) | 48.2 ± 5.8 |
| Mitral regurgitation, N (%)        |
| Absent                           | 5 (8.2)  |
| Discreet                         | 43 (70.5) |
| Mild/moderate                    | 12 (19.7) |
| Moderate/severe                  | 1 (1.6)  |
| Intraventricular delay, ms (mean ± SD) | 67.8 ± 57.8 |
| Interventricular delay, ms (mean ± SD) | 144.1 ± 89.3 |

AV: atrioventricular; SD: standard deviation; NYHA: New York Heart Association; RV: right ventricle; LV: left ventricle.
p = 0.816) and during the study period (r = 0.053, p = 0.684). Similarly, there was no correlation between the distance walked with the duration of RV stimulation (r = 0.099, p = 0.448), total duration of PM use (r = 0.057, p = 0.664), LVEF (r = 0.071, p = 0.877), LVDD (r = 0.161, p = 0.216), and the duration of the stimulated QRS complex (r = 0.057, p = 0.664) (Chart 3).

Chart 4 indicates the lack of association between the distance walked and gender (p = 0.121), mode of pacing (p = 0.821), position of the electrode in the RV (p = 0.928), or presence of maternal autoantibodies (p = 0.288).

Discussion
Congenital AV block can be adequately treated only with cardiac pacing. Considering its rarity, pathophysiology, and multiple clinical events it, presents peculiarities that make it difficult to standardize a routine care. Furthermore, there is no consensus as to the best time for PM implantation, pacing
Table 3 – Cardiorespiratory parameters measured before and after the six-minute walk test according to the type of pacemaker in use

| Measured parameters | VVIR mode | DDDR mode | p value |
|---------------------|-----------|-----------|---------|
| **Before the test** |           |           |         |
| Heart rate (bpm)    | 73.3 ± 12.2 | 75.1 ± 13.3 | 0.599   |
| Systolic pressure (mmHg) | 111.2 ± 11.7 | 111.2 ± 7.1 | 0.994   |
| Diastolic pressure (mmHg) | 75.0 ± 12.1  | 74.3 ± 7.2  | 0.804   |
| Oxygen saturation (%) | 97.6 ± 1.3  | 96.7 ± 1.7  | 0.028   |
| Borg scale           | 1.0 ± 0.1  | 1.3 ± 1.4  | 0.230   |
| **After the test**   |           |           |         |
| Heart rate (bpm)    | 95.2 ± 24.7 | 86.8 ± 16.6 | 0.141   |
| Systolic pressure (mmHg) | 116.7 ± 11.1 | 114.9 ± 10.7 | 0.553   |
| Diastolic pressure (mmHg) | 78.1 ± 11.6  | 77.1 ± 9.4  | 0.717   |
| Oxygen saturation (%) | 97.5 ± 1.6  | 97.1 ± 1.7  | 0.344   |
| Borg scale           | 2.2 ± 2.0  | 2.0 ± 2.0  | 0.727   |

Chart 3 – Correlation between the predicted distance walked in the six-minute walk test and age at the time of PM implantation (A), age during the study (B), duration of RV pacing (C), total period of PM use (D), LVEF (E), and LVDD (F).
mode, or access route to be used. Among the difficulties in patient monitoring, the inability to identify those who will develop late onset cardiomyopathy and severe heart failure has been the most important.

The selection criteria used in this study allowed the formation of a homogeneous group with isolated CAVB maintained with chronic RV pacing. Their preoperative characteristics exemplify the diversity of clinical presentations, in which 27.9% of the individuals presented with asymptomatic bradycardia and had marked differences in age during the first PM implantation, varying between a few days of life until 20 years of age. Although the ECG showed complete AV block in 95.2% of the patients, there was a large variation in the type of PM used, and patients with ventricular pacing represented 65.6% of the cases. The clinical improvement reported in the literature was confirmed in this study, with only 4.9% of the patients showing heart failure symptoms and only 8.2% requiring the use of cardiovascular medication.

There is evidence that chronic RV pacing may have deleterious effects on the LV function. The delayed activation, particularly of the free wall of LV, in relation to the interventricular septum, has been reported as an important cause of decreased efficiency of contraction, leading to increased volume, geometry changes and dysfunction of the LV. The population evaluated comprised individuals without cardiac defects, except CAVB, and represented an excellent model for understanding the effects caused by cardiac dyssynchrony induced by cardiac pacing, considering that, in addition to the normal cardiac anatomy, intraventricular impulse conduction is also normal in most cases. In the present study, we evaluated the primary factors related to poor clinical and functional outcomes, including age at the first PM implantation, pacing mode used, site of RV pacing, duration of cardiac pacing, duration of the PM-stimulated QRS complex, presence of dyssynchrony on echocardiography, and the presence of maternal autoantibodies.

In this scenario, the walk test can greatly contribute to the early detection of clinical worsening by allowing an objective assessment of functional capacity. The 6MWT is considered a submaximal test used to assess functional

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Chart 4 – Comparison between the predicted distance walked in the six-minute walk test and gender (A), pacing mode (B), position of the electrode in the RV (C), and presence of anti-Ro/SSA autoantibodies in patients’ mothers (D).
capacity, in view of the global and integrated responses of the systems involved during exercise (cardiorespiratory system, systemic and peripheral circulation, neuromuscular units, and muscle metabolism). The 6MWT can be performed by children, young people, older people with fragilities or other limitations, and by those who cannot be evaluated through standardized bicycle or treadmill maximal tests. Moreover, it is a quick and inexpensive way to measure the physical exercise capacity, and is safe, valid, and reproducible.

In the present study, despite the large age variation of individuals at the time of test application, most of them had a good functional capacity and walked distances greater than 80% of the predicted value, and 29.5% of the subjects walked a distance greater than that estimated by the equation. Moreover, a strong correlation was observed between the total distance covered and the distance predicted. On the other hand, the walk test did not correlate with any of the predictors of poor outcome in the study group.

With regard to the mode of pacing, in addition to the hemodynamic effects inherent to the loss of AV synchrony when ventricular PMs are used, the use of AV PMs enables individuals to take advantage of the physiological response of the heart rate because ventricular pacing is synchronized with spontaneous P waves. However, no difference was observed between the functional capacity of patients with AV PMs and that of patients with ventricular PMs. The tendency of increased heart rate variation between the initiation and completion of the walk test in patients with ventricular PMs modulated by sensors compared with that in patients with AV PMs modulated by spontaneous P waves may suggest that sensors may overestimate the need to adjust the heart rate.

Several equations for predicting the walking distance for normal populations have been proposed. One of the most commonly used is based on adults aged between 40 and 80 years. However, the option to use the Brazilian equation as a parameter of normality in the present study was justified by the fact that our sample comprised young subjects, with a physique different from international standards. The validity of this equation was tested in 85 subjects aged 41 ± 13 years, who walked 571 ± 74 meters versus a predicted distance of 575 ± 38 meters, which represented 99.6 ± 11.9% of the predicted value. In the present study, although the distance walked was smaller than expected, there was a significant correlation between the predicted and the walked distance, and the values obtained were similar to those achieved by normal subjects. These findings suggest that chronic RV pacing did not significantly limit the functional capacity of individuals with CAVB.

To the best of our knowledge, the study sample was the largest in which the functional capacity of a cohort of children and young adults with ICAVB and artificial PMs was evaluated after a long follow-up period in a single cardiology center. Recently, the functional capacity of 16 children with ICAVB was evaluated, 3 of which had not yet been subjected to PM implantation. Despite the small sample size, the authors found no differences between exercise capacity in the two groups.

Study limitations

The present study has limitations related to the cross-sectional analyses, such as the lack of a preoperative assessment of the functional capacity of the study group. Similarly, the lack of a control group prevented the formulation of more consistent hypotheses on the actual effects of PM implantation on the daily lives of patients. The rarity of this condition limits the design of clinical studies aimed at comparing outcomes before and after PM implantation, even in multicenter projects. The longitudinal follow-up, associated with clinical, laboratory, and detailed echocardiographic investigations, may provide more robust evidence on the possible deleterious effects of conventional PMs on the outcomes of individuals presented with isolated CAVB.

Some considerations need to be made in the interpretation of our results. The 6MWT does not determine peak oxygen consumption or allow the identification of the causes underlying potential physical exercise limitations, and this task is more appropriately performed using cardiopulmonary exercise testing. Therefore, the information provided by the 6MWT should be considered complementary to the cardiopulmonary exercise test but not a replacement. On the other hand, the walk test has been widely used to measure clinical outcomes in randomized studies with very large populations of patients with implantable electronic cardiac devices and therefore, can serve as a fast and objective measure of functional capacity and even as a prognostic marker of mortality and hospitalization in patients with heart failure. Additionally, it has been shown that the 6MWT correlates with the NYHA functional class, peak oxygen consumption, and life quality scores.

Conclusion

The functional capacity of children and young adults with isolated congenital AV block and right ventricular pacing was satisfactory and compatible with their clinical evaluation. However, the walk test failed to identify individuals with worse cardiac function and morphology outcomes or factors associated with poor outcome.

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Author contributions

Conception and design of the research and Analysis and interpretation of the data: Oliveira Júnior RM, Costa R; Acquisition of data: Oliveira Júnior RM; Statistical analysis: Alves LBO; Obtaining financing: Costa R; Writing of the manuscript:
Oliveira Júnior RM, Silva KR, Kawauchi TS, Costa R; Critical revision of the manuscript for intellectual content: Oliveira Júnior RM, Silva KR, Crevelari ES, Martinelli Filho M, Costa R.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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