Original Article

Correlation between C-Reactive Protein in Peripheral Vein and Coronary Sinus in Stable and Unstable Angina

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Abstract

Background: High sensitivity C-reactive protein (hs-CRP) is commonly used in clinical practice to assess cardiovascular risk. However, a correlation has not yet been established between the absolute levels of peripheral and central hs-CRP.

Objective: To assess the correlation between serum hs-CRP levels (mg/L) in a peripheral vein in the left forearm (LFPV) with those in the coronary sinus (CS) of patients with coronary artery disease (CAD) and a diagnosis of stable angina (SA) or unstable angina (UA).

Methods: This observational, descriptive, and cross-sectional study was conducted at the Instituto do Coração, Hospital das Clinicas, Faculdade de Medicina, Universidade de São Paulo, and at the Hospital Beneficência Portuguesa de Sao Paulo, where CAD patients referred to the hospital for coronary angiography were evaluated.

Results: Forty patients with CAD (20 with SA and 20 with UA) were included in the study. Blood samples from LFPV and CS were collected before coronary angiography. Furthermore, analysis of the correlation between serum levels of hs-CRP in LFPV versus CS showed a strong linear correlation for both SA (r = 0.993, p < 0.001) and UA (r = 0.976, p < 0.001) and for the entire sample (r = 0.985, p < 0.001).

Conclusion: Our data suggest a strong linear correlation between hs-CRP levels in LFPV versus CS in patients with SA and UA. (Arq Bras Cardiol. 2015; 104(3):202-208)

Keywords: C-Reactive Protein; Coronary Artery Disease; Angina, Stable; Angina, Unstable; Coronary Sinus.

Introduction

The investigation of biological markers to assess the risk of cardiovascular disease is one of the greatest challenges of medicine in recent decades, particularly in cardiology. These markers include glucose, creatinine, renin, low-density lipoprotein cholesterol, leukocytes as well as inflammatory markers such as lipoprotein phospholipase A2, interleukin 6, tumor necrosis factor-alpha, intercellular adhesion molecule, vascular cell adhesion molecule, monocyte chemoattractant protein-1, and selectin, among others.

More recently, high sensitivity C-reactive protein (hs-CRP) has been introduced as an inflammatory marker[1,2] to assess endothelial assault[3-5] and destabilization of atherosclerotic plaques[6-8].

Several studies using hs-CRP suggest that it may be an important biological marker for identifying higher-risk cases[9-14].

It is known that the synthesis of CRP is mainly hepatic[3,15], and some studies have reported the extrahepatic CRP synthesis in inflamed tissues[7,8,16,17]. If inflamed coronary arteries are the source of CRP in patients with coronary atherosclerosis, one hypothesis is that CRP levels in the cardiac sinus would be greater than those in the systemic circulation.

Therefore, the aim of this study was to compare serum hs-CRP levels (absolute values) in a peripheral vein in the left forearm (LFPV) with those found in the coronary sinus (CS) in patients with coronary artery disease (CAD) and a diagnosis of stable angina (SA) or unstable angina (UA).

Methods

Study approval and ethical considerations

This study was approved by the Science Committee and the Ethics Committee for Research Projects (CAPPesq) of InCor, HC–FMUSP, and Hospital Beneficência Portuguesa de São Paulo. All patients participating in the study signed a free informed consent form. The study was conducted in accordance with the Declaration of Helsinki.

Study characteristics

This observational, descriptive, and cross-sectional study was conducted at Instituto do Coração (InCor) at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, and at the Hospital Beneficência Portuguesa de São Paulo, where CAD patients referred to the hospital for coronary angiography were evaluated. Of these, 40 patients who fulfilled the selection criteria were included in the study and were classified into two groups: SA (n = 20) and UA (n = 20).

Selection of study participants

Inclusion criteria were SA[18], UA[19], stenosis diameter ≥ 70% in one of the main coronary arteries, normal left ventricular systolic function at rest (LVEF ≥ 55% calculated using the modified Simpson's method) observed via echocardiogram (ECHO), age between 40 and 75 years, normal sinus rhythm in electrocardiogram (ECG), and normal troponin I level (with high-sensitivity detection).

To eliminate the conditions that could be associated with elevated CRP levels, the following exclusion criteria were used: patients who underwent ablation, electrophysiological examination, or percutaneous coronary intervention < 3 months; history of alcohol abuse or abstinence from alcohol < 3 months; anemia; stroke < 3 months; bradycardia or tachycardia; congenital cardiopathy; cancer < 5 years; general or cardiac surgery < 3 months; peripheral arterial occlusive disease or carotid disease; diabetes mellitus; aortic dissection; chronic inflammatory disease, infectious or non-infectious acute inflammatory disease or trauma < 3 months; chronic renal failure (creatinine level ≥ 1.5 mg/dL); uncontrolled systemic arterial hypertension (SAH); hypo- or hyperthyroidism; acute myocardial infarction < 3 months; liver failure; cardiomyopathy; obesity; pneumopathy; smoking history, or abstinence from smoking < 3 months; previous organ transplant; drug therapy with glucocorticoids, immunosuppressants, or non-steroidal anti-inflammatory drugs < 3 months; valvopathy or congestive heart failure.

Laboratory assays and blood sample collection

The initial assessment comprised routine laboratory quantification of alanine aminotransferase (ALT), creatinine, glucose, complete blood count, thyroid-stimulating hormone (TSH), and troponin I, following routine methodologies used in the centers involved in the study as well as quantitative coronary angiography, ECHO, and ECG.

Blood samples were collected in the hemodynamics room with the patient lying supine at rest for at least 60 min. After fasting for 12 h, the last dose of statin (10 mg rosuvastatin), nitrate, or acetylsalicylic acid (ASA) was administered at least 11 h and 20 min before blood sample collection, which was performed between 7:20 a.m. and 10:10 a.m. on the following day.

All the blood samples were collected from LFPV (peripheral sample) through direct venipuncture and from CS (central sample) through direct catheterization before a contrasting agent, nitrate, or heparin was administered; the collected samples were transferred to 5-mL Vacuette® serum-separating tubes (Greiner Bio-One, Americana, São Paulo, Brazil).

Quantitative coronary angiography

The access points for coronary angiography included the right femoral artery and right radial artery. The position of the CS catheter was confirmed by immediately injecting the contrasting agent after blood sample collection (Figure 1).

Next, coronary angiography was performed using standardized projections, and the results of this examination indicated the degree of severity of stenosis. No complications occurred during coronary angiography or during blood sample collection from LFPV or CS.

Quantification of C-reactive protein

Serum samples were analyzed on the same day using high-sensitivity methodology, and CRP was quantified using an automated BN II Systems® equipment and the Cardio Phase hs-CRP® Kit (Siemens Healthcare Diagnostics Products, Marburg, Germany).

The reference value to assess the risk of vascular disease was < 1.0 mg/L. The detection limit of the method was 0.15 mg/L, and the coefficient of variation was 7.6% at a concentration of 0.4 mg/L.

Statistical analysis

Sample size was calculated on the basis of the Pearson correlation coefficient (r). Our hypothesis was that the correlation between hs-CRP levels in LFPV *versus* CS would be above 0.70. Based on the estimated correlation of 0.70, power of 80%, and a significance level of 5%, the sample size was obtained for each group (20 patients with UA and 20 with SA).

The quantitative variables were analyzed by calculating the means ± standard deviations, and for the qualitative variables, absolute and relative frequencies (%) were calculated.

The Shapiro–Wilk test was used to assess whether hs-CRP levels conformed to a normal distribution. CRP was analyzed by logarithmic transformation to achieve data normality.

To study the influence of the two factors on the mean values of the studied variables, two-way analysis of variance (ANOVA) was used. The means were compared using Student's *t*-test and proportions were calculated using the chi-square test or Fisher's exact test.

To correlate the hs-CRP levels in LFPV *versus* CS, the Pearson correlation coefficient was used. A simple linear regression model was used to obtain a predictor model.

The values obtained in each statistical test were considered significant when $p < 0.05$. All calculations were performed using Statistical Package for the Social Sciences (SPSS Inc®, Chicago, IL, United States) software, version 17.0.
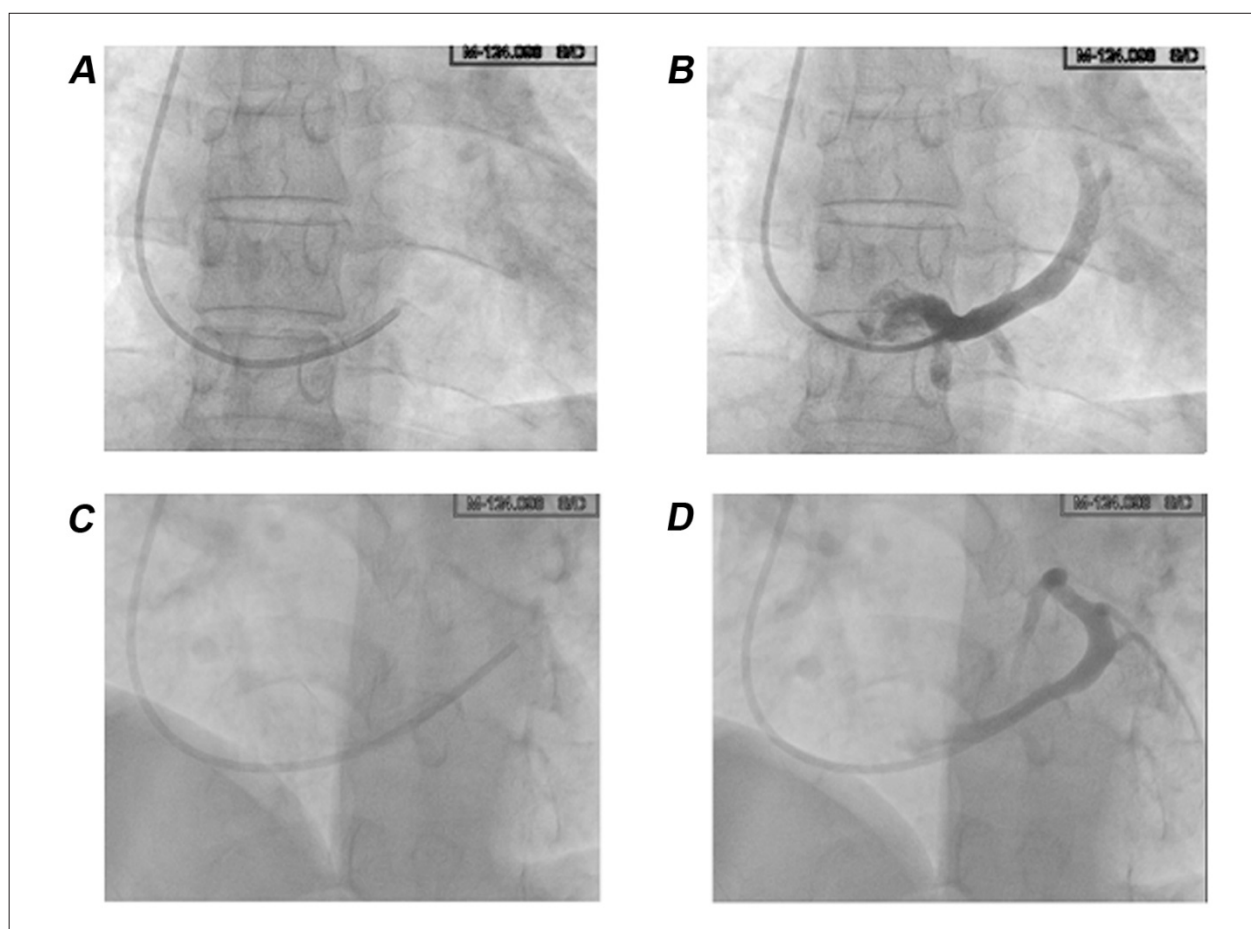
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Figure 1 – *Catheter in the coronary sinus in antero-posterior projection (A) and left anterior oblique view (C). Angiogram of the coronary sinus in antero-posterior projection (B) and left anterior oblique view (D).*

Results

Between November 2011 and September 2012, 40 patients presenting with atherosclerotic CAD and diagnosed with angina pectoris were evaluated and classified into two groups, SA (n = 20) and UA (n = 20), thereby forming the sample groups for this study.

The analysis of patients with SA and UA revealed no significant difference in their baseline characteristics (Table 1).

According to the laboratory evaluation criteria, there was also no significant difference between patients with SA and those with UA when the levels of ALT, creatinine, glucose, TSH, troponin I, and complete blood count were compared.

Considering that all the patients presented with symptomatic CAD, the prescribed medications (ASA, calcium channel blockers, beta-blockers, angiotensin receptor blockers, clopidogrel, diuretics, statins, angiotensin-converting enzyme inhibitors, and nitrates) were maintained. No significant differences were observed between patients with stable and unstable angina after treatment with these medications, with the exception of nitrates. The use of nitrates was justified by the greater intensity and frequency of angina pectoris in patients with UA 16 (80%) when compared with those with SA 5 (25%), with $p < 0.001$ (Table 2).

ANOVA was used to test the difference and to assess the possible impact of hs-CRP levels in patients with each type of angina. No interactive effect was observed between the two types of angina and the use of nitrates on hs-CRP levels from LFPV ($p = 0.559$) and CS ($p = 0.532$), and there was no significant difference in LFPV ($p = 0.762$) or CS ($p = 0.856$) between the groups treated or untreated with nitrate (Table 3).

Considering the lack of significant difference between patients with SA and UA for the baseline characteristics, effects of medications, and laboratory evaluation criteria, patients were also analyzed as a whole.

The analysis of the correlation between serum hs-CRP levels from LFPV versus CS showed a strong linear correlation for both patients with SA ($r = 0.993$, $p < 0.001$) and those with UA ($r = 0.976$, $p < 0.001$; Figure 2B) and for the entire sample ($r = 0.985$, $p < 0.001$; Figure 2C).

Table 1 – Baseline Characteristics of study participants

Variable	Total (n = 40)	Stable angina (n = 20)	Unstable angina (n = 20)	p
Age (years)	59.25 ± 9.34	59.50 ± 9.12	59.00 ± 9.79	0.868
Sex: male, n (%)	26 (65.0)	13 (65.0)	13 (65.0)	1.000
BMI (kg/m²)	26.00 ± 2.98	25.77 ± 3.29	26.24 ± 2.69	0.621
Ex-smoker, n (%)	25 (62.5)	12 (60.0)	13 (65.0)	0.744
Alcohol abuse, n (%)				
Ex-drinker, never, rarely	31 (77.5)	16 (80.0)	15 (75.0)	1.000
Mild to moderate alcohol abuse	9 (22.5)	40 (20.0)	5 (25.0)	
SAH, n (%)	29 (72.5)	16 (80.0)	13 (65.0)	0.288
Systolic blood pressure (mmHg)	122.50 ± 10.00	120.75 ± 11.27	124.25 ± 8.47	0.274
Diastolic blood pressure (mmHg)	73.88 ± 7.88	75.00 ± 6.07	72.75 ± 9.39	0.374
Heart rate (bpm)	64.65 ± 10.43	63.75 ± 10.45	65.55 ± 10.60	0.592

Ex-smoker: abstinence from tobacco > 3 months; ex-drinker: abstinence from alcohol > 3 months; rare alcohol use: ≤ 1 dose/month; light alcohol use: male or female ≤ 3 doses/week; moderate alcohol use: woman, 4–7 doses/week; man, 4–14 doses/week. Data are presented as means ± standard deviation, and percentage.

Table 2 – Medications used by patients at the time of the study

Medication	Stable angina (n = 20)	Unstable angina (n = 20)	p
ASA, n (%)	18 (90)	18 (90)	1.000
CCB, n (%)	4 (20)	6 (30)	0.465
Beta blocker, n (%)	14 (70)	14 (70)	1.000
ARB, n (%)	5 (25)	6 (30)	0.723
Clopidogrel, n (%)	7 (35)	9 (45)	0.519
Diuretic, n (%)	6 (30)	4 (20)	0.465
Statin, n (%)	13 (65)	14 (70)	0.736
ACE, n (%)	7 (35)	10 (50)	0.337
Nitrate, n (%)	5 (25)	16 (80)	< 0.001

ASA: acetylsalicylic acid; CCB: calcium channel blocker; ARB: angiotensin receptor blocker; ACE: angiotensin-converting enzyme inhibitor.

Table 3 – Levels of hs-CRP (mg/L) in LFPV and CS in patients with and without use of nitrate in stable and unstable angina

hs-CRP	Stable angina (n = 20)		Unstable angina (n = 20)	
	With nitrate	Without nitrate	With nitrate	Without nitrate
LFPV	3.11 ± 2.53	2.93 ± 2.83	3.13 ± 3.61	2.68 ± 1.83
log	0.82 ± 0.96	0.44 ± 1.33	0.65 ± 0.99	0.77 ± 0.78
CS	2.84 ± 2.33	2.67 ± 2.58	2.72 ± 3.30	2.35 ± 1.54
log	0.72 ± 0.93	0.38 ± 1.27	0.47 ± 1.04	0.66 ± 0.75

ANOVA−LFPV: interaction: p = 0.559; nitrate: p = 0.762; angina: p = 0.850. ANOVA−CS: interaction: p = 0.532; nitrate: p = 0.856; angina: p = 0.971. Data are presented as mean ± standard deviation and logarithmic transformation (log).
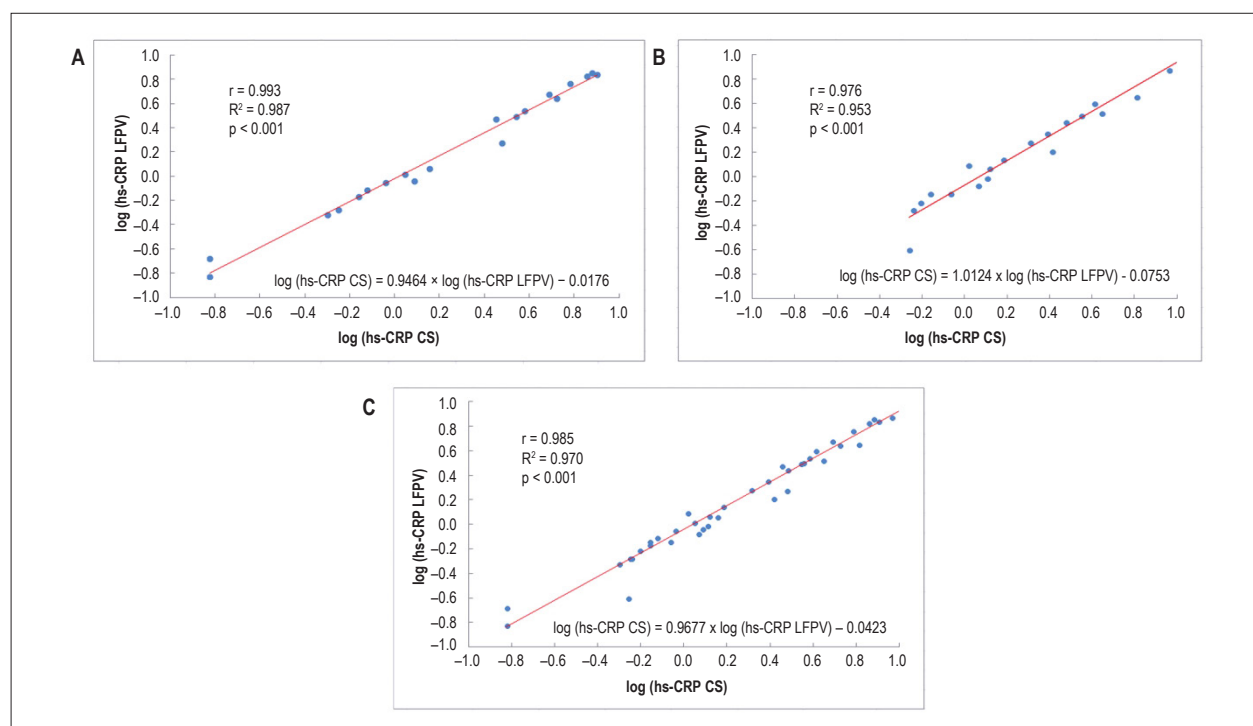
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Figure 2 – *Linear correlation between the logarithmic hs-CRP levels in LFPV versus CS in patients with stable angina (A), unstable angina (B), and in the entire sample (C).*

Discussion

The understanding that atherosclerosis is a chronic inflammatory disease with complex and autoimmune pathogenesis[20,21] has mobilized researchers to search for an ideal marker or a predictor of cardiovascular disease risk. To date, hs-CRP is used in clinical practice and has been reported in several studies[2,9 -11]. However, its prognostic significance and its role as a marker or predictor of coronary risk are debatable. In this respect, Sposito et al[22] did not find good sensitivity of serum CRP for the detection of inflammation in patients with acute myocardial infarction with ST-segment elevation; 70% of these patients exhibited a value of < 1.0 mg/L.

Although CRP has been known as an inflammatory marker since 1930[23], it also seems to be nonspecific. However, this fact does not decrease its importance[15]. CRP levels must always be used and interpreted based on the patient's clinical data, just as temperature, another non-specific parameter, is clinically important[15].

Other factors are associated with the inflammatory process and can be measured in several ways. One factor is the temperature change in the atherosclerotic plaque or coronary/myocardial trunk[24-26], which could affect hs-CRP levels. We did not check this parameter, but it was expected that inflammation would affect hs-CRP levels in CS[26], a finding observed in our study.

According to Buffon et al[27], generalized coronary inflammation occurs in the endothelium of different coronary arteries, regardless of the plaque location. On the other hand,

it is noteworthy that one third of the blood flow through CS comes from the posterior vein, draining the blood from the right coronary artery (RCA)[28]. In our study, we had only five patients (three with SA and two with UA) with isolated stenosis in RCA. Therefore, the impact on blood flow in RCA in CS was very low.

To the best of our knowledge, this is the first study that examined the correlation between the absolute levels of hs-CRP in LFPV *versus* CS in patients presenting with symptomatic CAD and with SA or UA.

To address the main objective of the study, the correlation between hs-CRP levels in LFPV *versus* CS in patients with SA or UA was assessed and the Pearson correlation coefficient was calculated. This analysis showed a strong linear correlation and an almost perfect correlation between these levels, clearly shown by the linear regression line, where the correlation coefficient was significant and close to 1 (Figures 2A and 2B).

Our data suggest that the strong correlation observed separately in patients with SA or UA was maintained in the entire sample (40 patients with CAD and angina pectoris) (Figure 2C), thereby drawing our attention because if increased local temperature is associated with the inflammatory process, and this process in turn is related to increased levels of hs-CRP, why were the peripheral blood hs-CRP levels (LFPV) the same as those obtained from the CS? The half-life of CRP in plasma is 19 hours[7]. Considering that coronary flow is approximately 5% of the cardiac output, even at rest, the additional increase in extrahepatic CRP on coronary circulation during the few minutes of coronary transit should be insignificant.

Wang et al[29] "compared the gradients of hs-CPR levels between the CS−aortic root and peripheral vein−aortic root," in patients with acute and chronic CAD (SA and UA). Their results indicated no difference in the gradients of hs-CRP levels between the coronary and systemic circulation. However, the study limitations may have affected the analysis of UA because they did not eliminate the possibility of acute myocardial infarction without ST-segment elevation through the determination of troponin, which can be a risk factor for increased hs-CRP levels[30].

The results of our study, unlike those of other authors[29,31], showed that hs-CRP levels in LFPV reflected the levels in CS, and therefore levels in the coronary circulation. This result could have future implications in clinical practice and research in order to avoid invasive techniques for blood sample collection from CS, which at present is considered the ideal location for assessing inflammatory markers and coronary circulation[31], considering that the hs-CRP levels found in LFPV and CS were similar and showed a strong linear correlation.

Considering the results presented herein, three formulas can be used to calculate hs-CRP levels in CS using the data from LFPV in patients with SA or UA or in the entire sample, with no difference between the groups with SA and UA.

We recognize the limitations of our study and its clinical applicability to all patients owing to the exclusion criteria involving patients with 100% suspected or known CAD referred to coronary angiography and patients having received at least one dose of statin immediately before the examination. These limitations may have contributed to the underestimation of the actual hs-CRP levels by interfering in the assessment of their absolute levels but not in the correlation between the levels in LFPV *versus* CS.

Conclusion

Our data suggest that in patients with CAD diagnosed with SA or UA, serum hs-CRP levels in LFPV *versus* CS showed a strong linear correlation.

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Leite WF, Ramires JAF, Moreira LFP, Strunz CMC, Mangione JA; Acquisition of data: Leite WF, Mangione JA; Statistical analysis: Leite WF, Moreira LFP; Obtaining financing and Writing of the manuscript: Leite WF, Ramires JAF.

Potential Conflict of Interest

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

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Study Association

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