Metalloproteinases-2 and -9 Predict Left Ventricular Remodeling after Myocardial Infarction

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Abstract

Background: The role of serum metalloproteinases (MMP) after myocardial infarction (MI) is unknown.

Objective: The aim of this study was to evaluate the role of serum MMP-2 and -9 as predictors of ventricular remodeling six months after anterior MI.

Methods: We prospectively enrolled patients after their first anterior MI. MMP activity was assayed 12 to 72 hours after the MI. An echocardiogram was performed during the hospitalization and six months later.

Results: We included 29 patients; 62% exhibited ventricular remodeling. The patients who exhibited remodeling had higher infarct size based on creatine phosphokinase (CPK) peak values (p = 0.037), higher prevalence of in-hospital congestive heart failure (p = 0.004), and decreased ejection fraction (EF) (p = 0.007). The patients with ventricular remodeling had significantly lower serum levels of inactive MMP-9 (p = 0.007) and significantly higher levels of the active form of MMP-2 (p = 0.011). In a multivariate logistic regression model, adjusted by age, CPK peak, EF and prevalence of heart failure, MMP-2 and -9 serum levels remained associated with remodeling (p = 0.033 and 0.044, respectively).

Conclusion: Higher serum levels of inactive MMP-9 were associated with the preservation of left ventricular volumes, and higher serum levels of the active form of MMP-2 were a predictor of remodeling 6 months after MI. (Arq Bras Cardiol. 2013;100(4):315-321)

Keywords: Matrix Metalloproteinase 2; Matrix Metalloproteinase 9; Myocardial Infarction; Ventricular Function, Left / physiopathology.

Introduction

Ventricular remodeling, defined as alterations in ventricular geometry, function, size, composition, and mass, have been associated with poor long-term outcomes after myocardial infarction (MI)[1-6]. Thus, an understanding of the pathophysiological alterations that are involved in these processes is essential for the development of effective myocardial infarction management strategies.

The cardiac extracellular matrix is critical for maintaining the structural integrity of the heart and is composed of structural elements, such as collagen, and other proteins, such as fibronectin, proteoglycans and matricellular proteins. An important component of this extracellular matrix is a family of extracellular matrix degrading enzymes, the metalloproteinases (MMPs). MMPs are a family of more than 25 species of zinc-dependent proteases that are essential for normal tissue remodeling and are involved in a number of pathological conditions, such as cancer and inflammatory and cardiovascular diseases. Specific MMPs are expressed in cardiac cells such as myocytes, fibroblasts, endothelial cells, smooth muscle cells and macrophages. These enzymes are synthesized as inactive zymogens and are secreted into the extracellular matrix as proenzymes of pro-MMPs, which remain quiescent until the propeptide domain is cleaved. Numerous MMPs, including gelatinases (MMP-2 and MMP-9), may be associated with cardiac alterations following various injuries[7].

The role of the MMPs in the cardiac remodeling process has been studied[8-25]. However, the role of gelatinases as predictors of remodeling in patients with MI remains to be elucidated. Therefore, the aim of this study was to evaluate the role of serum MMP-2 and -9 as predictors of ventricular remodeling in patients with anterior MI six months after the coronary occlusion.

Methods

All procedures were approved by the ethics committee of our institution, and all participants provided their written consent. Between December, 2009 and July, 2010, consecutive patients with anterior myocardial infarction were prospectively recruited.

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Acute MI was diagnosed in the presence of the two following criteria: persistent angina pectoris for ≥ 20 min and ST-segment elevation for ≥ 2 mm in ≥ 2 contiguous precordial leads or the presence of a left bundle branch block[26]. Acute MI was later confirmed based on the elevation of cardiac enzymes of more than twice the upper limit of the normal range.

The exclusion criteria were as follows: active malignancy, infection, end-stage cardiac, pulmonary, or hepatic disease, pregnancy, age < 18 years, atrial fibrillation, previous myocardial infarction, and valve disease.

At admission, data on patient characteristics, including waist circumference, body mass index, age, gender, heart rate, cardiovascular risk factors, concomitant diseases, adverse events, medical treatment and data regarding symptoms and pre-hospital delay, were recorded. Our definition of diabetes mellitus was based on clinical features and a fasting glucose level of ≥ 126 mg / dL on two separate occasions or ongoing treatment for the disease. Systemic arterial hypertension was considered to be present if the systolic blood pressure was > 140 mm Hg and / or the diastolic blood pressure was > 90 mm Hg. Dyslipidemia was identified according to the National Cholesterol Education Program (NCEP) III guidelines as total cholesterol levels ≥ 200 mg /dL, or HDL < 40 mg/ dL for men and < 50 mg/dL for women, or a triglycerides level ≥ 150 mg/dL. Obesity was defined as a body mass index (BMI) ≥ 30 kg/m^2.

For the adverse events during the follow-up period, stable angina was diagnosed based on the presence of cardiac symptoms in a pattern that remained constant in presentation, frequency, character and duration over time, and coronary disease was diagnosed using coronary angiography. Unstable angina was diagnosed based on the presence of new cardiac symptoms and positive electrocardiogram (ECG) findings with normal biomarkers or a changing pattern of symptoms and positive ECG findings with normal biomarkers and coronary disease at coronary angiography. All other pre-specified definitions utilized in this study were similar to those in previous clinical trials[27].

Serum MMP activity was assayed 12 to 72 hours after MI and was determined as reported by Tyagi et al[28]. Briefly, samples for analysis were prepared by dilution in extraction sample buffer consisting of the following: 50 mM Tris, pH 7.4; 0.2 M NaCl; 0.1% Triton X; and 10 mM $CaCl_2$. Then, they were diluted in application sample buffer consisting of the following: 0.5 M Tris, pH 6.8; 100% glycerol; and 0.05% bromophenol blue. The samples were loaded into the wells of 8% SDS-polyacrylamide gels containing 1% gelatin. Electrophoresis was conducted with a Bio-Rad apparatus at 80 V for 2 hours and was stopped when the bromophenol blue arrived at the bottom of the gel. The gel was removed and washed 2 times with 2.5% Triton-X-100 and then washed with 50 mM Tris, pH 8.4. The gel was then incubated at 37°C overnight in activation solution consisting of the following: 50 mM Tris, pH 8.4; 5 mM $CaCl_2$; and $ZnCl_2$. The staining was performed for 2 hours with 0.5% Coomassie blue and destaining in 30% methanol and 10% acetic acid until clear bands over a dark background were observed. The staining and destaining were performed at room temperature on a rotatory shaker. The gels were photographed, and the intensity of the gelatinolytic action (clear bands) was analyzed in a UVP, UV, White Darkhon image analyzer.

The echocardiogram assessment was completed by three cardiologists. However, the same operator analyzed the same patient during the index hospitalization (approximately 3-5 days after admission) and at the 6-month follow-up. The echocardiograph was an HDI 5000 Sono CT model (Philips Medical Systems, Botheee, Washington, USA) that was equipped with a 2.0 to 4.0 MHz probe capable of acquiring second harmonic, tissue, pulsed, continuous, and color Doppler, as well as one- and two-dimensional mode images. With individuals positioned in the left lateral decubitus and monitored with an electrocardiographic lead, the following echocardiographic views were obtained: the short parasternal axis to measure the ventricles, aorta and left atrium and the apical two, four and five chambers to evaluate the cavities and the systolic and diastolic functions of the ventricles. All measurements were performed in accordance with the recommendations of the American Society of Echocardiography/European Association of Echocardiography[29]. The average of three measurements was calculated for each variable. In the study group, intraobserver and interobserver variabilities were < 5% and < 10%, respectively.

The left atrium volume was obtained using the Simpson method with the apical two- and four-chamber views. The LV systolic function was evaluated by measuring the ejection fraction according to the Simpson method. The LV diastolic function was evaluated by measuring the following: early (E-Wave) and late (A-Wave) diastolic mitral inflow velocity; the E- to A-Wave ratio; the E-Wave deceleration time (EDT); the isovolumic relaxation time (IVRT); the early (E' Wave) and late (A' Wave) diastolic mitral annulus velocity (the average of the septal and lateral walls) using tissue Doppler; and the E/E' ratio. Ventricular remodeling was defined as an increase of at least 15% in the LV end-systolic or end-diastolic volume at the 6-month follow-up[30].

The comparisons between the groups were completed with Student's *t* tests when the data presented a normal distribution. For a non-normal distribution, the comparisons between the groups were completed using Mann-Whitney *U* tests. The data were expressed as the mean ± standard deviations or the median with the 25th and 75th percentiles. A Chi-squared test was used to compare the categorical variables. The predictive values were analyzed using a multivariate logistic regression. Data analysis was completed with SigmaStat for Windows v2.03 (SPSS Inc, Chicago, IL). The significance level was considered to be 5%.

Results

A total of 37 consecutive patients were evaluated. Four patients were lost to follow-up, and four patients died. Thus, 29 patients were analyzed at admission and at the 6-month follow-up.

In our study, 62% of the patients demonstrated ventricular remodeling. The patients were divided in two groups using the clinical and echocardiographic data: patients with remodeling and patients without remodeling.

The clinical characteristics are shown in Table 1. Patients with remodeling presented with higher total plasma creatine kinase (CPK) levels and a higher incidence of heart failure. The remaining variables showed no differences between the groups.

Table 1 - Demographic, clinical and laboratory data

Variables	Left ventricular remodelling		p value
	Yes (n=18)	No (n=11)	
Age (yrs)	59.6 ± 10.8	57.6 ± 12.0	0.661
Male, n (%°)	10 (56)	9 (82)	0.234
SR, n (%°)	12 (67)	4 (33)	0.143
DM, n (%°)	5 (28)	2 (18)	0.677
Dyslipidemia, n (%°)	15 (83)	11 (100)	0.268
Smoking, n (%°)	8 (44)	3 (27)	0.449
BMI (kg/m^2)	28.0 ± 4.35	27.0 ± 5.36	0.596
CK (U/L)	5130 (1456-8711)	1104 (579-4227)	0.037
CK-MB (U/L)	441 ± 225	334 ± 385	0.236
Heart failure, n (%°)	13 (72)	1 (9)	0.004

SR: systemic hypertension; DM: diabetes mellitus; BMI: body mass index; CK: creatine phosphokinase; CK-MB: creatine phosphokinase – MB. Data are expressed as the mean ± SD or the median (including the lower and upper quartiles).

The medications utilized during the hospitalization are shown in Table 2. Patients with remodeling required more diuretics than patients without remodeling. The remaining variables showed no differences between the groups. After 6 months, the rates of patients using aspirin, angiotensin-converting enzyme inhibitors, and beta-blockers were 100%, 93% and 80%, respectively, with no difference between the groups.

The initial echocardiographic data are shown in Table 3. Patients with remodeling presented with smaller ejection fractions and EDTs than patients without remodeling. The remaining variables showed no differences between the groups.

Patients with remodeling presented lower levels of inactive MMP-9 than patients without remodeling (Figure 1). On the other hand, the levels of the active form of MMP-2 were higher in patients with remodeling (Figure 2).

In the multivariate analyses, inactive MMP-9 was an independent predictor of the preservation of LV volumes. Each 1 unit increase in the inactive MMP-9 level was associated with a 35% decrease in the odds of ventricular remodeling. In addition, the active form of MMP-2 was an independent predictor of remodeling. Each 1 unit increase in the MMP-2 level was associated with a 39% increase in the odds of ventricular remodeling (Table 4).

Table 2 - Treatment data during hospitalisation

Variables	Left ventricular remodelling		p value
	Yes (n=18)	No (n=11)	
FT, n (%)	5 (28)	3 (27)	1.000
PA, n (%)	13 (72)	6 (54)	0.432
TIMI 2-3 n (%)	15 (83)	10 (91)	0.291
ASA, n (%)	18 (100)	11 (100)	1.000
Clopidogrel, n (%)	18 (100)	11 (100)	1.000
GP IIb/IIIa I, n (%)	11 (61)	4 (36)	0.362
Heparin, n (%)	18 (100)	11 (100)	1.000
Diuretic, n (%)	14 (78)	3 (27)	0.018
ACE i, n (%)	18 (100)	11 (100)	1.000
Beta-blockers, n (%)	17 (94)	11 (100)	1.000
Nitrates, n (%)	9 (50)	2 (18)	0.125
Spironolactone, n (%)	8 (44)	2 (18)	0.234
Statins, n (%)	18 (100)	11 (100)	1.000

FT: fibrinolytic therapy; PA: primary angioplasty; TIMI: Trombolysis in Myocardial Infarction post-reperfusion; ASA: acetylsalicylic acid; GP IIb/IIIa I: glycoprotein IIb/IIIa inhibitor; ACE i: angiotensin converting enzyme inhibitor.

Table 3 - Echocardiographic data (3 to 5 days after admission)

Variables	Left ventricular remodelling		p value
	Yes (n=18)	No (n=11)	
LA (mm)	42.3 ± 6.29	41.5 ± 4.21	0.716
LVEDD (mm)	49.3 ± 6.47	50.6 ± 3.76	0.540
LVSD (mm)	32.4 ± 5.87	33.1 ± 2.62	0.712
IVS (mm)	11.4 ± 2.24	10.8 ± 1.93	0.425
LVWT (mm)	11.1 ± 1.80	10.7 ± 1.71	0.588
E-wave (cm/s)	70.2 ± 16.1	72.9 ± 28.8	0.754
A-wave (cm/s)	90.0 (74.3 – 93.3)	82.0 (71.0 – 87.0)	0.289
E/A	0.80 (0.65 – 1.19)	0.82 (0.70 – 0.88)	1.000
IVRT (ms)	111 (90.0 - 126)	116 (104 -124)	0.651
EDT (ms)	178 ± 56.6	230 ± 47.2	0.025
EF (%)	0.43 ± 0.10	0.55 ± 0.10	0.007

LV: left ventricle; LA: left atrium; LVEDD: LV end-diastolic dimension; LVSD: LV systolic dimension; IVS: interventricular septum; LVWT: LV posterior wall thickness; E-Wave: peak velocity of early ventricular filling; A-Wave: peak velocity of transmitral flow during atrial contraction; IVRT: isovolumetric relaxation time; EDT: E-Wave deceleration time; EF: ejection fraction. Data are expressed as the mean ± SD or the median (including the lower and upper quartiles).

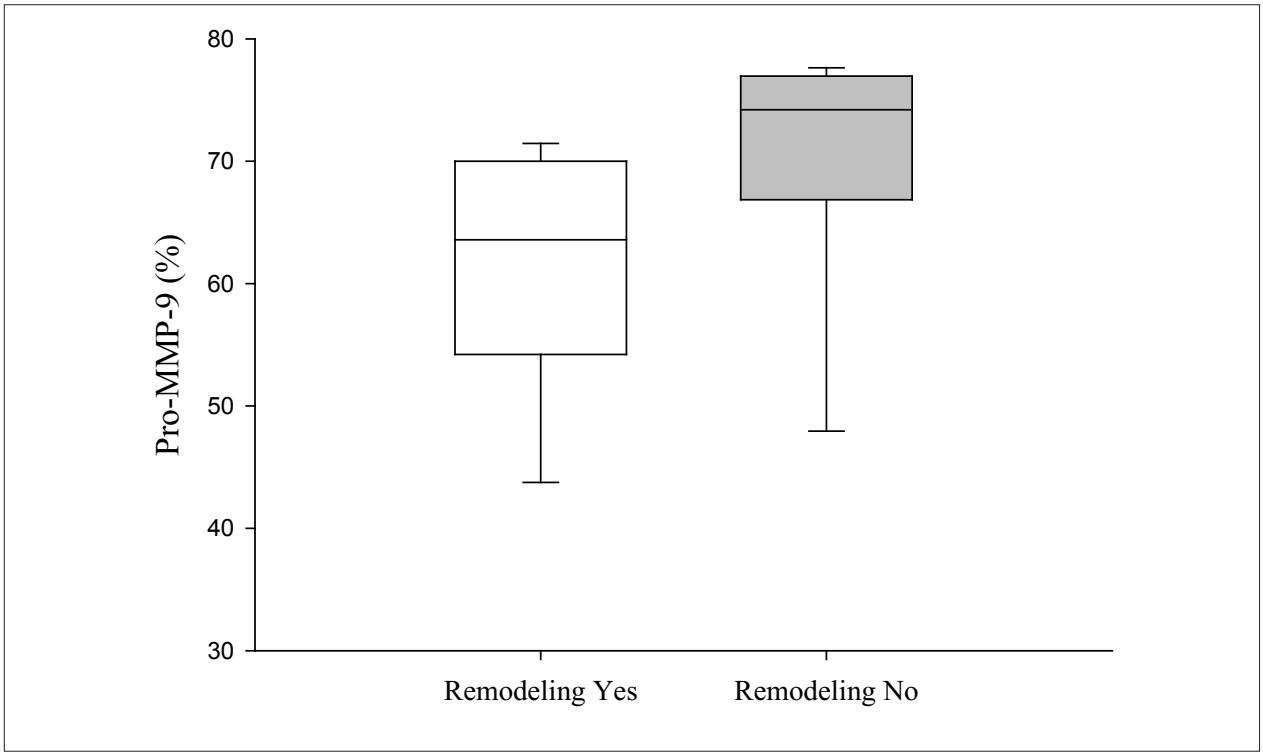

Figure 1 - *Levels of inactive MMP-9 (92 kDa) based on the presence of ventricular remodeling 6 months after myocardial infarction. p = 0.007.*

Discussion

The aim of this study was to evaluate the role of serum MMP-2 and -9 as predictors of ventricular remodeling in patients with anterior MI six months after the coronary occlusion. Our results suggest that higher levels of the inactive form of MMP-9 were independently associated with the preservation of left ventricular volumes, and higher levels of the active form of MMP-2 were an independent predictor of ventricular remodeling 6 months after anterior MI.

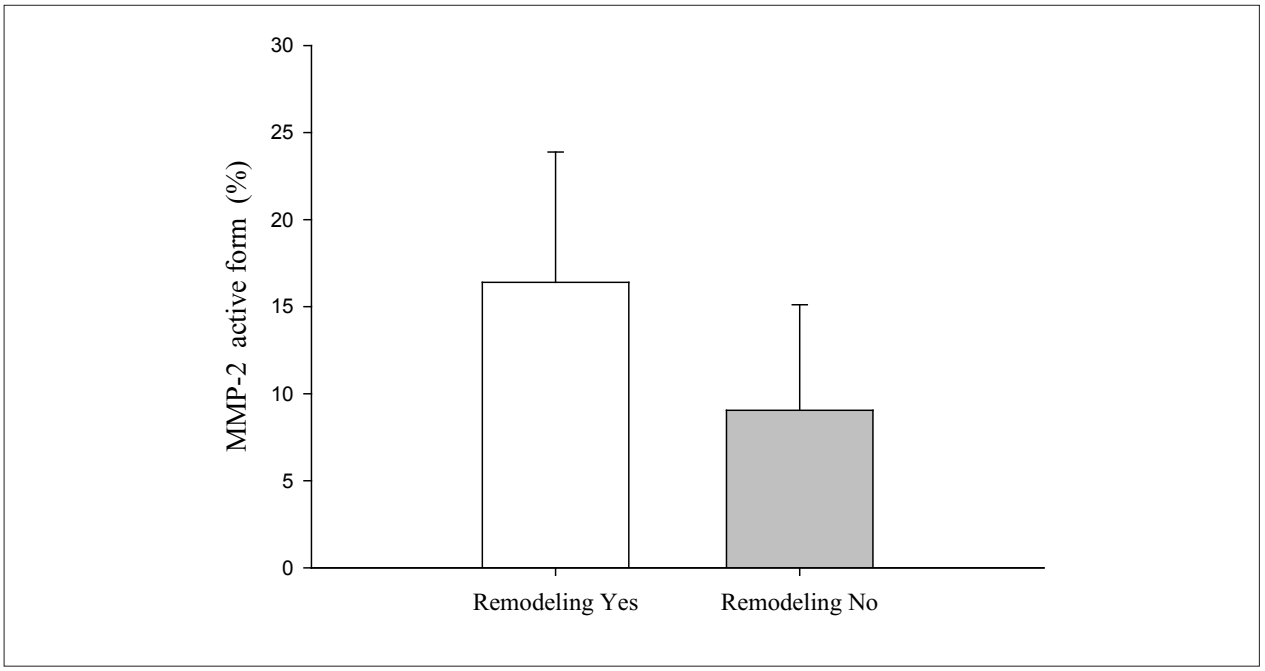

Figure 2 - *Levels of active MMP-2 (64 kDa) based on the presence of ventricular remodeling 6 months after myocardial infarction. p = 0.011.*

Table 4 - Logistic regression analysis for MMP-2 and MMP-9 values as predictors of left ventricular remodeling

	Odds Ratio	95% CI	p Value
Inactive MMP-9*	0.74	0.55 – 0.99	0.044
MMP-2 active form*	1.39	1.03 – 1.88	0.033

** Adjusted for age, heart failure, ejection fraction, and creatine phosphokinase levels.*

Regardless of the complexity of the remodeling process, after MI, the term is frequently used as a synonym for ventricular dilation[1-6]. Importantly, ventricular remodeling is associated with cardiac rupture, ventricular aneurysm, an increased risk of progressive ventricular dysfunction, and cardiovascular death after MI. Therefore, several variables have been used to predict the remodeling process in the acute phase of MI, such as infarct size, infarct location, previous infarct, wall stress, neurohumoral activation, diabetes mellitus, hypertension, decreased ejection fraction, and signs of heart failure[31-35].

It is accepted that the cardiac extracellular matrix is critical for maintaining the structural integrity of the heart. Indeed, extracellular matrix degradation by MMP has been associated with slippage of myocyte fascicles and left ventricular wall thinning. Extracellular matrix degradation paralleled by an abnormal collagen accumulation has been reported after MI, when left ventricular enlargement also occurs[36]. Likewise, the increased cardiac activity of MMP-2 and -9 was associated with cardiac remodeling and heart failure in several experimental studies[8-14]. In addition, the pharmacologic and genetic inhibition of MMP attenuated the development of heart failure in infarcted rats[9,13-16]. Thus, it is accepted that MMP can modulate the remodeling process in animal models.

Clinical studies have also demonstrated elevated serum levels of MMP-2 and -9 in patients with MI[17-21] and its association with clinical outcomes such heart failure, cardiogenic chock and death[22-24]. Therefore, there is solid evidence that MMP can modulate the remodeling process. However, the role of serum MMP-2 and -9 as predictors of VR in patients with anterior MI is less clear.

Considering the prognostic value of MMP-9 after MI, Kelly et al found that the active form of MMP-9 was associated with remodeling only if it was assessed in the first 12 hours following MI[20]. However, we must consider that many patients are not available in the very early period after MI. In our study, higher serum levels of inactive MMP-9, assayed 12 to 72 hours after MI, was a predictor of the preservation of LV volumes six months after the coronary occlusion. This phenomenon can be explained by the decreased transformation from the inactive form to the active form of MMP-9.

In relation to levels of MMP-2 as predictors of RV, Webb et al did not find an association between MMP-2 levels and LV dilation after the coronary occlusion[19]. The same results were found by Kelly et al[20]. On the other hand, in a study conducted by Squire et al, increased LV diameters

after MI were associated with decreased levels of MMP-2[25]. Finally, there was an association between active MMP-2 and cardiac remodeling in patients with anterior and inferior MI. Importantly, in that study, the MMP levels were assessed in blood that was obtained by cardiac catheterization, and the LV volumes were assessed by ventriculography during the first 30 days after MI[21]. In our study, serum levels of the active form of MMP-2, assessed 12 to 72 hours after MI, was an independent predictor of the remodeling process in patients with anterior MI.

Finally, we should consider the major limitations of this study. First, our study included a small sample of patients at a single hospital. However, we believe that our study added important data about the role of serum MMP-2 and -9 as predictors of cardiac remodeling after anterior MI. Therefore, our data suggest that MMP-2 and -9 might be useful clinical biomarkers of LV remodeling following infarction.

In conclusion, higher serum levels of inactive MMP-9 were associated with the preservation of left ventricular volumes, and higher serum levels of the active form of MMP-2 were a predictor of ventricular remodeling 6 months after anterior MI.

Author contributions

Conception and design of the research: Cogni AL, Minicucci MF, Zornoff LAM; Acquisition of data: Cogni AL, Farah E, Okoshi K, Matsubara BB, Zanati S, Haggeman R; Analysis and interpretation of the data: Cogni AL, Farah E, Minicucci MF, Azevedo PS, Okoshi K, Matsubara BB, Zanati S, Haggeman R, Zornoff LAM; Statistical analysis: Minicucci MF, Paiva SAR; Writing of the manuscript: Cogni AL, Azevedo PS, Paiva SAR, Zornoff LAM; Critical revision of the manuscript for intellectual content: Cogni AL, Minicucci MF, Azevedo PS, Paiva SAR, Zornoff LAM.

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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