

## BNP was Associated with Ischemic Myocardial Scintigraphy and Death in Patients at Chest Pain Unit

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### Abstract

**Background:** Recent studies have suggested that B-type Natriuretic Peptide (BNP) is an important predictor of ischemia and death in patients with suspected acute coronary syndrome. Increased levels of BNP are seen after episodes of myocardial ischemia and may be related to future adverse events.

**Objectives:** To determine the prognostic value of BNP for major cardiac events and to evaluate its association with ischemic myocardial perfusion scintigraphy (MPS).

**Methods:** This study included retrospectively 125 patients admitted to the chest pain unit between 2002 and 2006, who had their BNP levels measured on admission and underwent CPM for risk stratification. BNP values were compared with the results of the MPS. The chi-square test was used for qualitative variables and the Student t test, for quantitative variables. Survival curves were adjusted using the Kaplan-Meier method and analyzed by using Cox regression. The significance level was 5%.

**Results:** The mean age was  $63.9 \pm 13.8$  years, and the male sex represented 51.2% of the sample. Ischemia was found in 44% of the MPS. The mean BNP level was higher in patients with ischemia compared to patients with non-ischemic MPS ( $188.3 \pm 208.7$  versus  $131.8 \pm 88.6$ ;  $p = 0.003$ ). A BNP level greater than 80 pg/mL was the strongest predictor of ischemia on MPS (sensitivity = 60%, specificity = 70%, accuracy = 66%, PPV = 61%, NPV = 70%), and could predict medium-term mortality (RR = 7.29, 95% CI: 0.90-58.6;  $p = 0.045$ ) independently of the presence of ischemia.

**Conclusions:** BNP levels are associated with ischemic MPS findings and adverse prognosis in patients presenting with acute chest pain to the emergency room, thus, providing important prognostic information for an unfavorable clinical outcome. (Arq Bras Cardiol. 2015; 104(1):16-23)

**Keywords:** Natriuretic Peptide; Brain; Heart Failure; Myocardial Perfusion Imaging; Myocardial Ischemia.

### Introduction

Currently, several biomarkers are important tools for diagnosis, risk stratification and therapeutic decision making in cardiovascular diseases<sup>1-4</sup>. Brain Natriuretic Peptide (BNP), mainly synthesized by ventricular myocytes from a precursor, pre-pro BNP, is released by stimulating cardiac myocyte stretch, caused by pressure or volume overload in the heart<sup>5-7</sup>. The most studied use of BNP to date is in the diagnosis, prognosis and management of patients with heart failure (HF)<sup>2,7-15</sup>. Another emerging use of BNP is in the diagnosis and prognosis of patients with acute coronary syndrome (ACS). There is evidence that there is a direct release of BNP in response to ischemia, even in the absence of myocardial necrosis<sup>16-22</sup>. Myocardial perfusion scintigraphy (MPS) has been widely used as an important tool in decision making in patients with acute chest pain<sup>23-24</sup>. Its value in the diagnosis of

acute myocardial infarction (AMI) and in the prognosis of patients admitted with ACS has been well established<sup>25-27</sup>. Our group has recently demonstrated that ischemia detected by MPS was the major independent factor in predicting adverse events for patients admitted with acute chest pain to the emergency room<sup>24</sup>. Considering that the availability of complex imaging procedures in the emergency room is limited to reference centers and that the prevalence of ACS is high, this study aims to evaluate if the use of BNP at the chest pain unit (CPU) can determine adverse cardiac events in the medium term, as well as to evaluate its association with the MPS findings.

### Methods

#### Participants

We conducted a retrospective observational study and selected consecutive patients admitted to the CPU of a tertiary hospital from December 2002 to April 2006. Participants in this study were recruited from a consecutive cohort of patients admitted to the CPU complaining of "chest pain". This study was approved by the Research Ethics Committee of the Hospital Pró-Cardíaco under registration No. 137/2005. Signed Informed Consent was not required. This study had no external funding sources.

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### Blood analysis

Blood was collected on admission to the CPU, and the blood samples were centrifuged at 4000 rpm. BNP was measured in all samples by use of sandwich enzyme immunoassay technique (Alere Triage® BNP Test) with the lowest sensitivity of 5 pg/mL. The intra- and interassay coefficient of variation was lower than 10% for all assays.

### Myocardial Perfusion Scintigraphy

All patients underwent clinical investigation that consisted of performing ECG and MPS with physical or pharmacological stress (dipyridamole or adenosine or dobutamine), as well as measuring myocardial necrosis markers (troponin-I and CK-MB mass) and BNP. They were evaluated according to the institutional protocol of chest pain<sup>26</sup>. After the exclusion of AMI or high-risk unstable angina (UA), the patients underwent rest and stress MPS for coronary risk stratification. Those who did not undergo the two phases of the test and those with incomplete medical records were excluded from the study.

All the tests were carried out in a dual head gamma camera (Ecam-Duet Siemens, Milpitas, USA), with a low-energy and high resolution collimator with tomographic image acquisition (SPECT - Single Photon Emission Computed Tomography) gated with ECG, with 64 projections and a 64 x 64 matrix. After their acquisition, the images were reconstructed through back projection with a Butterworth filter, and processed using e-Soft (Emory Cardiac Toolbox™), an image processing software package. The analysis of global and segmental contractility and of ejection fraction was accomplished by using gated SPECT. The unit used the 17-segment myocardial segmentation model<sup>27</sup>. The tests were evaluated by two experienced physicians, certified in Nuclear Medicine and Cardiology.

Clinical data and the results of laboratory tests relative to the studied population were obtained from the patients' hospital files, which were considered the main data source. The following clinical variables were analyzed: sex, age, systemic arterial hypertension, dyslipidemia, smoking, sedentary lifestyle, diabetes mellitus, family history of coronary artery disease, obesity, history of AMI, and previous surgical myocardial revascularization (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

The scintigraphic variables were: the type of stress used, the number of segments showing reversible perfusion defects (ischemia) and fixed defects (fibrosis) on qualitative analysis, and quantification of these defects by using software (Cedars Sinai and Emory Cardiac Toolbox); analysis of global and segmental contractility and ejection fraction.

### Follow-up

We collected information on adverse events that took place after patients' discharge from hospital. The interventions (PTCA, CABG) performed during hospitalization were not considered as adverse events, but as a result of treatment. Follow-up was conducted via telephone with information obtained from patients, relatives, families or doctors, or via hospital records, when available. We collected information about events occurring after hospital discharge, the primary outcome being

death, and the secondary outcome, a combination of events, death and AMI. Acute myocardial infarction was defined as a new episode of chest pain lasting more than 20 minutes and requiring hospitalization, which was confirmed by the elevation of myocardial necrosis markers (creatine phosphokinase fraction MB [CK-MB] or Troponin I) or the appearance of Q waves on ECG and the need for reperfusion therapy with thrombolysis or emergency PTCA.

### Statistical analysis

The chi-square test or Fisher's exact test was used for categorical variables. To assess the continuous variables between the two groups, Student *t* test was used for independent samples. Multivariate analysis, to identify independent factors that simultaneously influence or explain the occurrence of events and to assess the simultaneous influence of clinical variables on events, was carried out using logistic regression. Stepwise regression with a significance level of 5% was used to select the factors. The event-free survival rate (neither primary nor secondary outcomes) was adjusted by the Kaplan-Meier method and Cox regression for analysis. Log-rank test was used to verify if there was significant difference in the event-free survival curve for primary and combined events stratified according to the MPS results. The difference was considered significant for a *p* value lower than 0.05, and highly significant for a *p* value lower than 0.01. The SPSS software (SPSS version 19.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

### Results

This study assessed 64 men and 61 women, whose mean age was 63.9 ± 13.8 years. Tables 1 and 2 show the reported symptoms on admission and the clinical characteristics of the population, respectively. Based on the MPS findings, 55 (44%) patients had ischemia, 34 of whom (61.8%) were men. Statistically significant difference was observed regarding sex (*p* = 0.035), smoking history (*p* = 0.003), history of diabetes (*p* = 0,04) and history of coronary heart disease (*p* < 0.001)]. These and other clinical characteristics are shown in Table 3. The absolute value of BNP was higher in patients with ischemia than in those with normal MPS (188.3 ± 208.7 versus 131.8 ± 88.6; *p* = 0.003), as shown in Figure 1.

Table 1 – Symptoms

	n	%
Chest pain A	06	4.8
Chest pain B	77	61.6
Chest pain C	24	19.2
Chest pain D	0	0
Dyspnea	11	8.8
Palpitation	04	3.2
Dizziness	05	4.0
Syncope	01	0.8

**Table 2 – Baseline characteristics**

	n	%
Hypertension	92	73.6
Diabetes	22	17.6
Dyslipidemia	70	56.0
Sedentary lifestyle	61	48.8
Obesity	24	19.2
Smoking	38	30.4
Menopause	25	20.0
Coronary disease	70	56.0

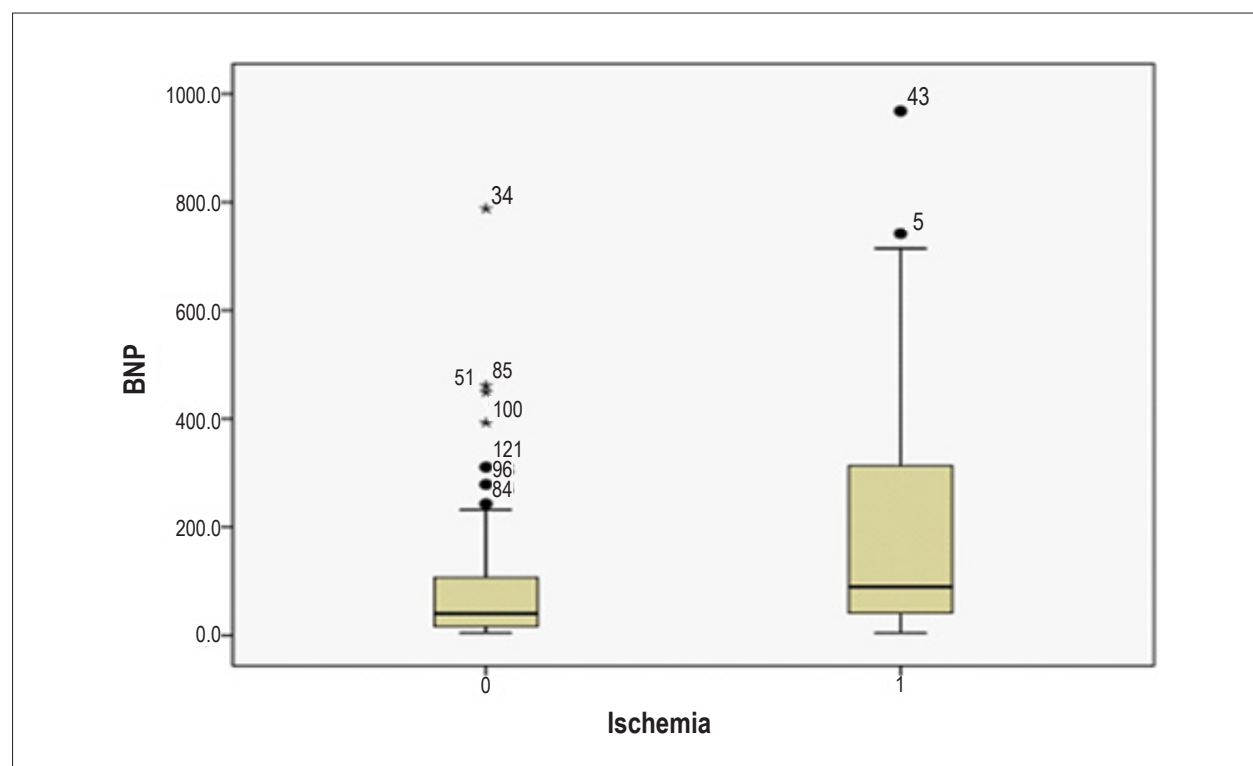
The mean ejection fraction on gated SPECT was  $62\% \pm 19\%$ , and an ejection fraction lower than 45% correlated with BNP levels greater than 80 pg/mL ( $p = 0.002$ ) and with ischemia on MPS (31% with ischemia had an ejection fraction lower than 45%,  $p = 0.000$ ).

Multivariate analysis showed that BNP greater than 80 pg/mL is a powerful independent marker for the diagnosis of ischemia on MPS (sensitivity = 60%, specificity = 70%, accuracy = 66%, PPV = 61%, NPV = 70%). An ejection fraction lower than 45% on gated SPECT correlated with neither ischemia on MPS ( $p = 0.12$ ) nor death on multivariate analysis ( $p = 0.9$ ).

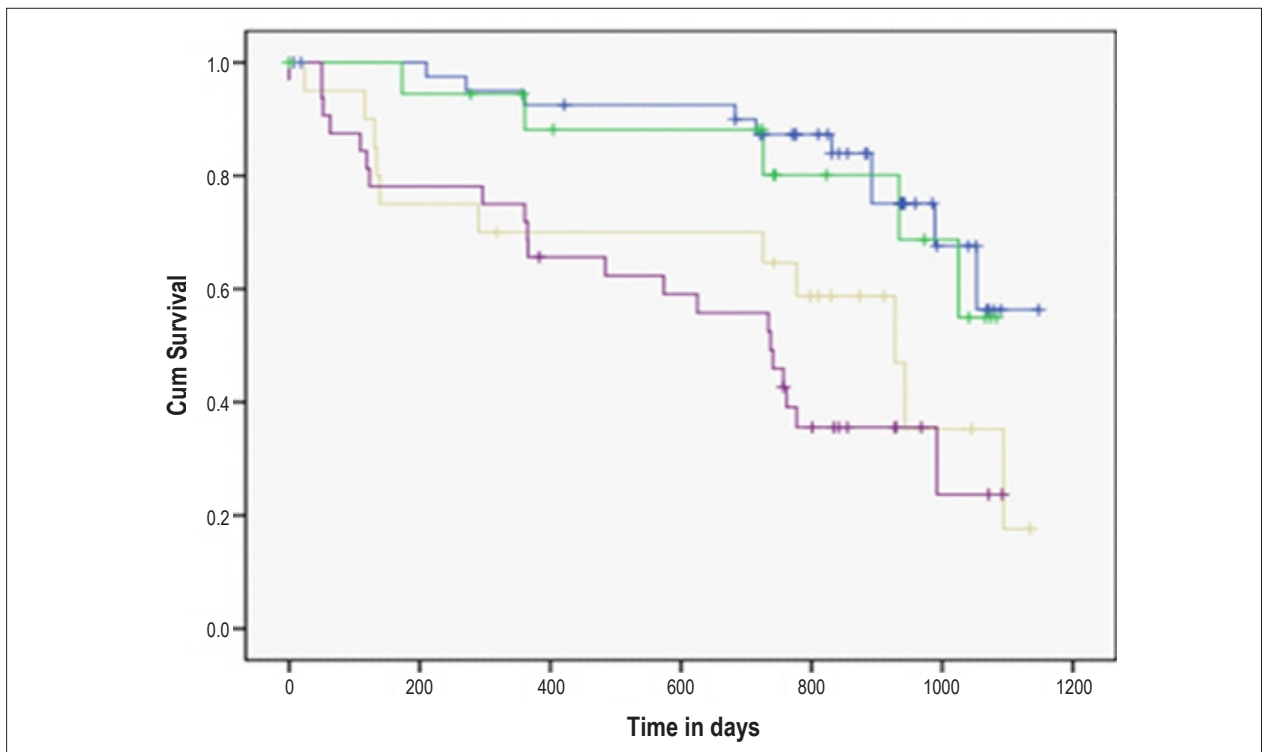
**Table 3 – Clinical characteristics correlated with ischemia**

	Ischemia				p value
	Yes		No		
	N	%	N	%	
Male	34	53.1	30	46.9	0.035
Hypertension	43	46.7	49	53.3	0.300
Dyspnea	05	45.5	06	54.5	0.900
Diabetes	14	63.6	08	36.4	0.041
Coronary disease	41	58.6	29	41.4	< 0.001
Obesity	11	45.8	13	54.2	0.800
Smoking	24	63.1	14	36.9	0.003
Dyslipidemia	33	47.1	37	52.9	0.420
Menopause	06	27.3	16	72.7	0.080
Sedentary lifestyle	25	41	36	59	0.500

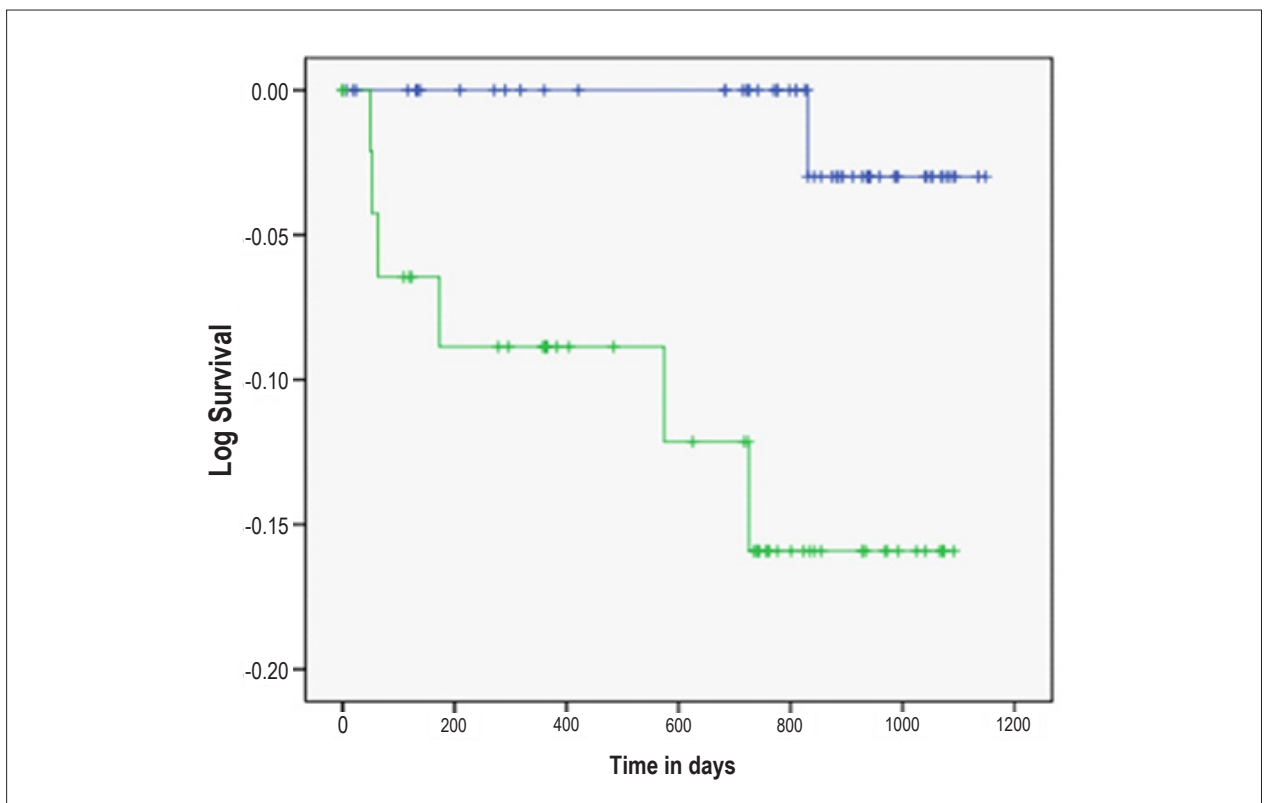
The prognosis analysis by use of logistic regression and survival curve showed that the presence of BNP greater than 80 pg/mL could predict medium-term death (RR = 7.29, 95% CI = 0.90 to 58.6;  $p = 0.045$ ) regardless of the presence of ischemia. The follow-up period was  $700.5 \pm 326.6$  days. The combination of ischemia and high BNP did not worsen the mid-term prognosis (Figures 2, 3 and 4).



**Figure 1 – Box plot showing dispersion of BNP levels according to the presence (1) or absence (0) of ischemia.**



**Figure 2** – Survival curve according to BNP levels and presence of ischemia. Blue line represents patients with no ischemia on MPS and BNP levels under 80 pg/mL. Green line represents patients with no ischemia and BNP above 80 pg/mL. Yellow line represents patients with ischemia on MPS and BNP levels under 80 pg/mL, and purple line represents patients with both ischemia on MPS and BNP levels above 80 pg/mL.



**Figure 3** – Survival curve according to BNP level. Blue line represents patients with BNP levels above 80 pg/mL and green line represents patients with BNP levels under 80 pg/mL.

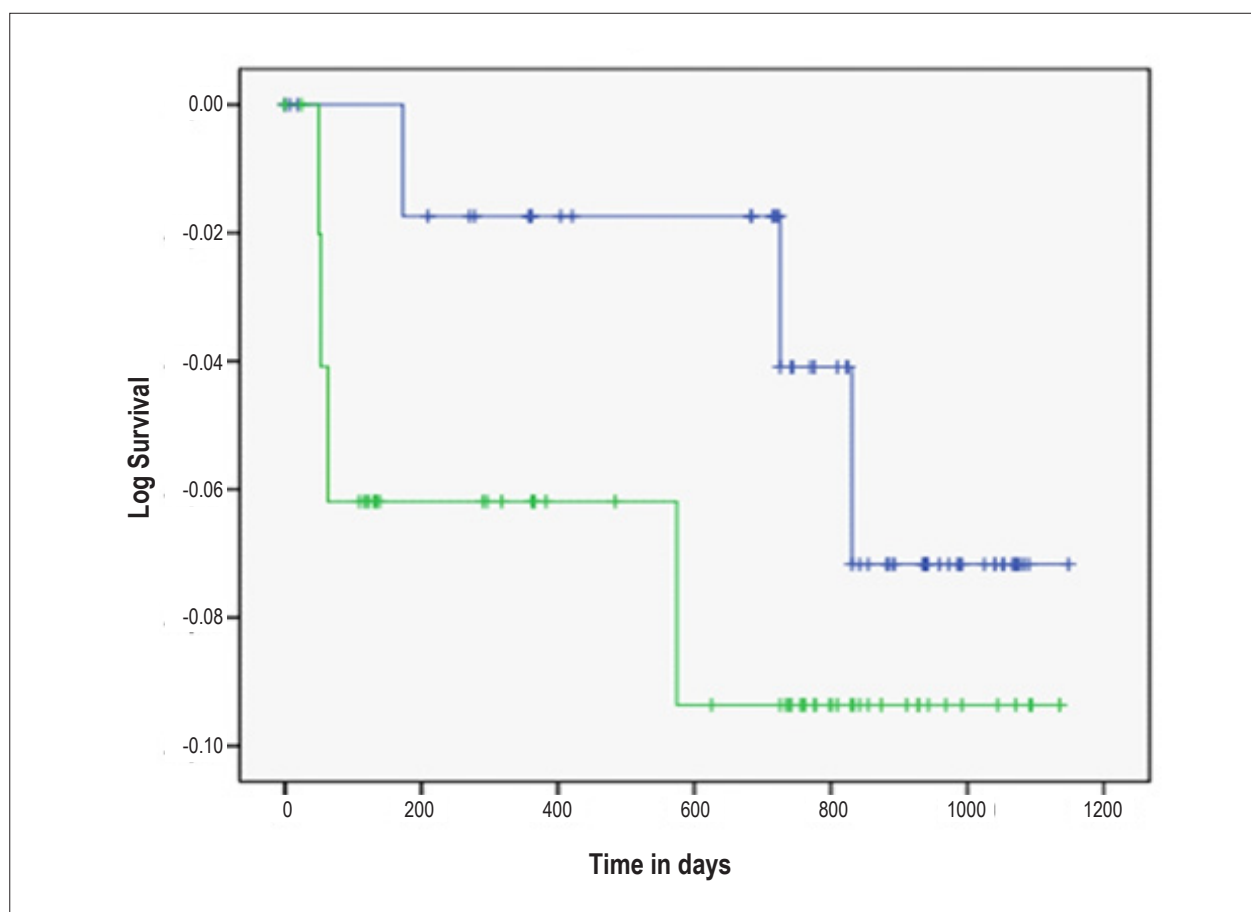


Figure 4 – Survival curve relative to presence of ischemia (green line) or absence of ischemia (blue line).

## Discussion

The past 30 years have seen a continuous search for new biomarkers for diagnosis, prognosis, risk stratification and therapeutic decision making in patients with chest pain in the emergency room. Epidemiology also shows importance in the search for new techniques that accelerate the diagnosis and avoid complications in patients at risk of cardiovascular disease, which currently occupies the first place in the morbidity and mortality rates worldwide<sup>28-30</sup>. A wide range of biomarkers has been evaluated in the context of cardiovascular diseases, such as adrenomedullin, natriuretic peptides (NT-pro ANP and NT-proBNP), co-pectin, choline, C-reactive protein (CRP), the ligand CD40 (CD40L), cystatin C (Cys C), fibrinogen, and, more recently, intermedin<sup>30,31</sup>. Despite the existence of several markers, BNP has proved to be one of the best diagnostic tools in the emergency room, not only as a screening test for patients with complaints of dyspnea, but also to assist in the diagnosis and prognosis of patients with chest pain<sup>12-14</sup>. Dao et al.<sup>32</sup> have demonstrated that BNP has a well-established role in the evaluation of patients with dyspnea of unknown etiology in the emergency room. In their study, BNP was measured in 250 patients who presented with dyspnea as a chief complaint in

the emergency department, and the results indicated a significant discrepancy between the BNP values in patients with and without a HF diagnosis. It is also important to highlight that BNP values of 80 pg/ml were highly sensitive and specific for the diagnosis of HF<sup>32</sup>.

Another applicability of BNP may be in the evaluation of ACS. Some studies have also shown that after AMI, a high BNP level is associated with more extensive infarctions, greater chance of ventricular remodeling, lower ejection fraction and a higher risk of HF and death<sup>33-36</sup>. Foote et al.<sup>37</sup> have suggested that exercise-induced ischemia and the measurement of plasma NT-pro-BNP and BNP levels before and immediately after symptom-limited exercise can distinguish between patients with and without ischemia, whereas ischemia is defined as a reversible defect on scintigraphy, with a high degree of accuracy. The hypothesis is that exercise-induced ischemia, can indirectly cause abnormalities of regional wall motion, resulting in increases in detectable BNP levels. Patients with induced ischemia compared with those without ischemia have higher elevations of NT-proBNP and BNP levels, corroborating that hypothesis. Thus, an exercise-induced increase in BNP can be considered a marker of induced ischemia, and this finding is more accurate in detecting

ischemia than ST-segment depression during exercise testing<sup>37</sup>. In addition, other studies have shown the prognostic value of BNP. Harrison et al.<sup>38</sup> have investigated whether BNP levels of patients arriving at the emergency department with acute dyspnea could be a predictor of future cardiac events. Those authors have concluded that in this population of patients with acute dyspnea, BNP values could be highly predictive of cardiac events at six months. Sabatine et al.<sup>16</sup> have also demonstrated the prognostic value of BNP in the context of ACS and observed that a high initial level of this peptide correlates with the risk of death, HF or myocardial infarction at 30 days and 10 months. In our study we found that BNP greater than 80 pg/mL was the most powerful independent marker for the diagnosis of ischemia on MPS. Furthermore, the presence of BNP levels greater than 80 pg/mL had a high predictive power for death, being associated with a 7-fold increase in the relative risk as compared with BNP levels below that value. Therefore our study, in agreement with previously published data, suggests that the implementation of BNP evaluation may be useful for risk stratification of patients with chest pain and suspected ACS without ST elevation and negative troponin<sup>39</sup>. An additional issue to be discussed is that, although our work demonstrated that elevated BNP levels correlated with poor prognosis, these levels have no additional value to predict adverse events in patients with ischemia. In a recent study, Nadir et al.<sup>40</sup> have demonstrated that BNP can identify ischemia better than troponin does, but have not demonstrated the values that are predictors of myocardial ischemia, which further enhances our study.

## Conclusions

The present study demonstrated that in patients admitted to the emergency department complaining of chest pain, who subsequently showed ischemia on MPS, had higher BNP levels than those with normal MPS, showing the close relationship of BNP as an independent marker of ischemia. Furthermore, we have demonstrated through analysis of

prognosis that BNP levels greater than 80 pg/mL were able to predict death, being a useful marker in that population.

## Author contributions

Conception and design of the research: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Acquisition of data: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Analysis and interpretation of the data: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Statistical analysis: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Obtaining Financing: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Writing of the manuscript: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT; Critical revision of the manuscript for intellectual content: Azevedo JC, Reis BCC, Barreto NMPB, F. Junior DS, Prezotti LS, Procaci VR, Octaviano VW, Volschan A, Mesquita ET, Mesquita CT.

## 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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