Prognostic Value of B-Type Natriuretic Peptide in the Mortality of Patients with Acute Coronary Syndrome

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Abstract

Background: The prognostic value of BNP in acute coronary syndrome (ACS) has been repeatedly assessed, but not completely well established. Literature data for establishing the best time for assessing BNP, be it on hospital admission or after coronary intervention, are controversial.

Objective: To analyze BNP in non-ST segment elevation ACS (NSTE-ACS) in the long term, and to assess the association between BNP (pg/ml), death, coronary anatomy, and TIMI Risk Score.

Methods: Forty patients with NSTE-ACS and troponin>0.50 ng/ml had their BNP levels measured on admission and 96 hours after, and were followed up for four years. The difference between the two measures was assessed by use of Wilcoxon test (p<0.05). The ROC curve was used to evaluate 96-hour BNP accuracy as a death predictor, and logistic regression was used to assess a possible confounding factor among 96-hour BNP, age, and outcome.

Results: There was an increase in the 96-hour BNP (148 on admission vs. 267 after 96 hours; p=0.04). Thirteen patients died. For the 300 pg/ml cutoff, 96-hour BNP was a death predictor (sensitivity, 92.30%; specificity, 77.80%; positive predictive value, 66.70%; negative predictive value, 95.50%). The area under the ROC curve was 0.92. A 7.4-time increase in the relative risk of death in four years was observed with a 96-hour BNP> 300 pg/ml (95% CI 1.90 a 29.30 p<0.01). An association between 96-hour BNP and TIMI Risk Score was observed (p<0.01).
An association was observed between the increase in 96-hour BNP and multivessel disease (p=0.02).

Conclusion: In NSTE-ACS with positive troponin, 96-hour BNP can be a tool for risk stratification. (Arq Bras Cardiol 2012;99(1):605-612)

Keywords: Prognosis; natriuretic peptides; acute coronary syndrome / mortality.

Introduction

In USA and Europe, approximately fifteen million people are admitted to emergency units each year with symptoms suggestive of acute coronary syndrome (ACS)[1]. Acute coronary syndrome is characterized by its complexity and multiple physiopathological causes, such as plaque rupture with acute thrombosis, progressive mechanical obstruction, unstable secondary angina, inflammation, and dynamic obstruction (coronary vasospasm)[2].

The strategy of multiple markers has recently been studied for ACS assessment, and includes, in addition to troponin as a myocardial necrosis indicator, other elements such as natriuretic peptides (BNP and NT pro-BNP) as hemodynamic stress markers, C reactive proteins a marker of inflammatory activity, and creatinine clearance as an indicator of endothelial injury[3].

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Aiming at refining prognosis and guiding clinical interventions, Antman et al.[4] have proposed the point score known as TIMI Risk Score for ACS patients. The synergism of this set of markers could constitute a useful tool for understanding the prognosis of such a heterogeneous syndrome. The use of statistics to analyze the prognosis predicted by BNP and NT pro-BNP has been demonstrated in non-ST elevation ACS (NSTE-ACS), including patients with neither clinical evidence of left ventricle failure nor increased myocardial necrosis markers (troponin)[5-6]. Studies have demonstrated the potential of BNP and NT pro-BNP for providing additional information to traditional markers of ischemia subendocardial or subepicardial lesions on electrocardiography and assessment of regional left ventricular wall motion abnormalities on 1D/2D transthoracic echocardiography) and of myocardial necrosis (troponin) in ACS[7].

Considering the heterogeneity of ACS and its impact on mortality worldwide and in Brazil, this study suggests the routine use of BNP after coronary intervention for risk stratification in NSTE-ACS with positive troponin, assessing the value of that peptide in the long-term prognosis of high-risk patients.

In addition, this study assesses the existence of an association between BNP and the three-vessel coronary anatomy, as well as the association between BNP and TIMI Risk Score.

Methodology

Study population

This single-center study assessed 46 consecutive patients with high-risk NSTE-ACS and positive troponin, admitted to the Chest Pain Unit (CPU) of the Hospital CopaD'Or, in the city of Rio de Janeiro, Brazil, from May 2003 to January 2004. Six patients were excluded from the study as follows: two because of death within the first 96 hours after admission, and four because of not undergoing invasive stratification. Forty patients completed the study.

The study follow-up extended over a period of four years after the patients' selection and consisted in the administration of a questionnaire by phone every six months. In case of an abnormal event, the study researchers were notified so that they could assess the event. This study was approved by the Committee on Ethics and Research of the institution.

Patient Selection

During the initial consultation at the emergency unit, the following inclusion criteria were considered:

a) Presence of NSTE-ACS and increased troponin I (>0.5ng/ml)[8] as a high-risk factor;

b) Admission to the CPU and transference to the Cardiac Intensive Care Unit within the first 24 hours of symptom onset, with monitoring of progress;

c) Invasive stratification in the first 24 hours after admission;

d) Signing the written informed consent.

After that, complementary tests were requested and the treatment strategy was defined.

The exclusion criteria were as follows:

a) Contraindication for angiographic study or indication of conservative treatment by attending physician;

b) Death within the first 96 hours after admission;

c) Presence of concomitant heart valvular disease;

d) Kidney failure defined as estimated creatinine clearance < 50ml/min, calculated by use of the Cockroft-Gault[9] formula;

e) Left ventricular dysfunction (EF≤50% by Simpson's rule), either symptomatic or not.

Procedures

Collection of blood samples for assessing BNP and troponin I. The Blood samples were collected to measure BNP on admission and 96 hours after that. The 96 hours following hospital admission were defined as the period in which BNP could indicate the final product of coronary intervention, being, thus, a more specific tool for analyzing long-term prognosis than BNP on admission. The immunofluorescence assay Triage BNP test (Biosite Diagnostics, San Diego, CA, USA) was used.

The Troponin I was assessed on admission and four hours after by using an enzymatic method (Dade Behring kit) and the Immulite device. The highest value was considered for the study. The reference value adopted was < 0.5ng/ml.

The TIMI Risk Score[4] of the patients was calculated by adding the points, according to the medical history and clinical presentation.

The risk factors for CAD, such as systemic hypertension, diabetes mellitus, dyslipidemia, obesity, and smoking, have been well defined in the medical literature[10].

The 12-lead ECG was performed on admission and four hours after that. Patients with ST-segment elevation on ECG were excluded. Later, ECG was repeated daily during stay at the Cardiac Intensive Care Unit.

All patients underwent transthoracic echocardiography within the first 12 hours of admission, according to the chest pain protocol of the institution where the study was conducted.

Invasive stratification with coronary angiography was performed within the first 24 hours after admission.

A lesion of the left main coronary artery ≥50% or a proximal lesion of the anterior descending (AD) and circumflex (CX) coronary arteries ≥70% was considered to correspond to an extensive myocardial area at risk for ischemia and multivessel disease.

Statistical analysis

The Wilcoxon test was used with a 95% confidence interval and a p value of <0.05 was considered significant for analyzing BNP levels on admission and 96 hours after that.

The Pearson chi-square test was used to analyze possible clinical characteristics involved with the outcome. The ROC curve was used to identify the best BNP cutoff point as a cardiac death predictor.

The Logistic regression analysis was used to assess a possible confounding factor among age, 96-hour BNP, and outcome.

Results

The population of this study consisted of 40 patients (men, 55.00%), with a mean age of 69.08±11.40 years. Table 1 shows the clinical, electrocardiographic, and echocardiographic characteristics of the group studied. Regarding the therapeutic strategy on hospital admission, twenty-three patients underwent coronary angioplasty, ten patients underwent myocardial revascularization, and seven patients underwent only clinical treatment.

The TIMI Risk Score of 75.00% of the patients ranged from 4 to 6, confirming the risk profile of the patients in this study.

A clear association of the TIMI Risk Score with the 96-hour BNP value was observed (p<0.01), but not with the BNP value measured on admission.

Figure 1 depicts a graph that clearly demonstrates the association between the TIMI Risk Score and the 96-hour BNP value.

Table 1 - Clinical, electrocardiographic, and echocardiographic characteristics of the population sample

Characteristics	Findings
Age (years)	69.08 ±11.40
Men (%)	55.00
Hypertension (%)	67.50
Diabetes mellitus (%)	25.00
Smoking (%)	25.00
Body Mass Index	25.05 [23.50 – 28.00]
Prior infarction (%)	35.00
TIMI Risk Score	4 [4 – 5]
T-wave inversion in electrocardiogram (%)	12.50
ST decrease in electrocardiogram (%)	55.00
Segmental alteration in echocardiogram (%)	77.50

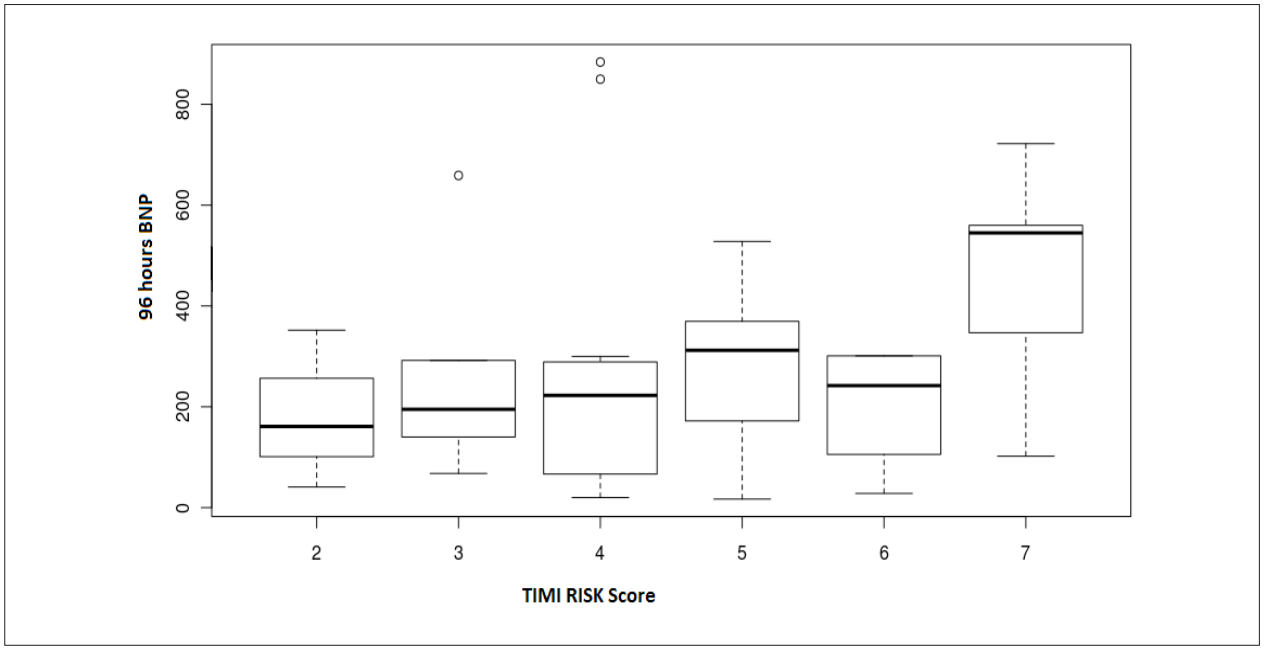

Figure 1 - *Association between the TIMI Risk Score and 96-hour BNP*

Analyzing the forty coronary angiographies, twenty-four (60.00%) met the above-specified criteria for an extensive myocardial area at risk for ischemia, while sixteen (40.00%) coronary angiographies lacked that finding.

In the presence of an extensive myocardial area at risk for ischemia (Table 2), an important increase in the prevalence of segmental dysfunction on echocardiography was observed (p=0.03), in addition to ECG alterations suggestive of myocardial ischemia (p=0.01).

Comparing the two BNP values (on admission and after 96 hours) and coronary artery anatomy, a significant difference (p=0.02) was observed in the BNP values (on admission and after 96 hours) in the group of patients with an extensive myocardial area at risk for ischemia. On the other hand, in the group of patients with no damage to the left main coronary artery or its equivalent, no significant difference was observed in the BNP values (p=0.06) (Figure 2).

During the four-year follow-up, thirteen patients died, four of whom had sudden death. The other nine patients died during hospitalization due to recurrence of ACS, the causes of death being as follows: sepsis, five patients; stroke, two; entero-mesenteric infarction, one; and heart failure, one patient.

Comparing the clinical and electrocardiographic findings of deceased patients and those of live patients after a four-year follow-up, only more advanced age could be related to

Table 2 - Alterations in ECG and echocardiogram, and association with the at-risk myocardium

Extent of the at-risk myocardium	n	Alterations in ECG (%)	Segmental alteration in the echocardiogram (%)
Yes	24	39.02	46.34
No	16	26.83	29.27

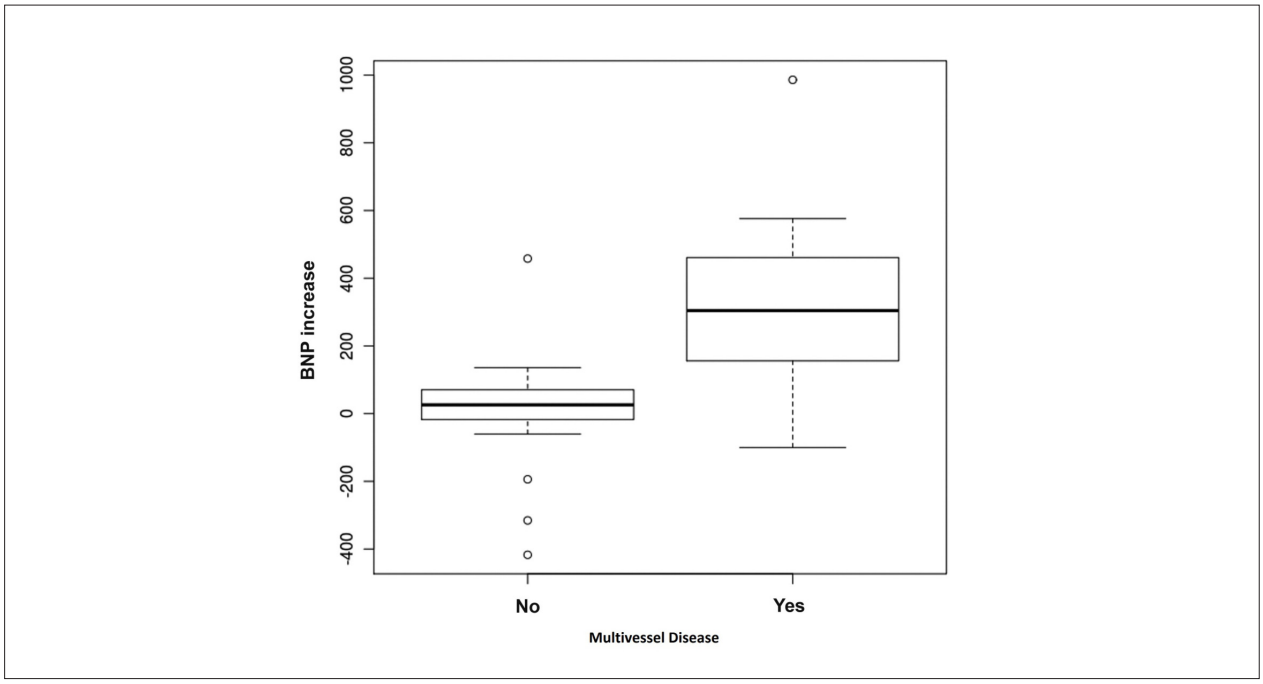

Figure 2 - *Increase in BNP level within 96 hours from admission vs. multivessel disease*

the death outcome (Table 3). The ROC curve showed that the 96-hour BNP cutoff point of 300.00 pg/ml most clearly distinguished patients at higher risk for death during the four-year follow-up. For that cutoff point, sensitivity was 92.30%, specificity was 77.80%, positive predictive value was 66.70%, and negative predictive value was 95.50%.

The area under the curve was 0.92, (95% CI 90.20→94.80; $p<0.01$), indicating good accuracy (Figure 3).

To assess a possible confounding factor among age, BNP, and outcome, logistical regression was used. For each ten-year increase in age, no contribution to the death outcome was observed. However, 96-hour BNP proved to be an important mortality predictor for the cutoff point of 300 pg/ml, with a ten-time increased risk ratio (Table 4). The analysis of the BNP accuracy on admission, that is, within 24 hours after the coronary event, did not reach significance. Assessing the cutoff point of 274 pg/ml, resulted in sensitivity of 46.20%, specificity of 85.20%, positive predictive value of 60.00%, and negative predictive value of 76.70%. The area under the curve was 0.65, which did not indicate good accuracy. As 96-hour BNP represents the result of the therapeutic intervention, we believe that, in our study, 96-hour BNP can be more specific than BNP on admission for the association with long-term prognosis.

We observed a relative risk of 7.44 (95% CI 1.89→29.28) in the group of patients with 96-hour BNP higher than 300.00 pg/ml. However, we meet a large CI, perhaps with a more significant number of patients, could to establish a better association with our findings.

Discussion

This study showed that the BNP measured 96 hours after admission, using 300 pg/ml as the cutoff point, associated with the significant relative risk of death of 7.44 (95% CI 1.89→29.28) during the four-year follow-up. The area under the ROC curve was 0.92, showing a good accuracy. This finding is in accordance with other studies in the literature, such as those by Weber et al. and Bassan et al.[11-15], showing the statistical power and importance of natriuretic peptides as predictors of cardiac death in ACS patients.

The age was the only variable that could be associated with outcome, although no relation is known to exist between age bracket and high serum BNP levels. Moreover, the logistic regression analysis has shown that age, 96-hour BNP, and outcome are not associated.

Table 3 - Clinical, electrocardiographic, and angiographic characteristics in the non-surviving and surviving groups

Characteristics	Non-Survivors (n=13)	Survivors (n=27)	p
Age (years)	74.90 ± 9.30	66.30 ± 11.40	0.02
Men n (%)	6 (46.10)	7 (25.90)	0.44
Smoking n (%)	0 (0)	10 (37.00)	0.72
Hypertension n (%)	9 (69.20)	18 (66.60)	1.00
Diabetes mellitus n (%)	4 (30.70)	4 (14.80)	0.40
Prior infarction n (%)	6 (46.10)	8 (29.60)	0.48
ST decrease n (%)	8 (61.50)	14 (51.80)	0.33
Left main coronary artery lesion n (%)	4 (30.70)	4 (14.80)	0.40
Anterior descending (AD) coronary artery lesion n (%)	8 (61.50)	15 (55.50)	0.13
Myocardial revascularization n (%)	3 (23.00)	7 (25.90)	1.00

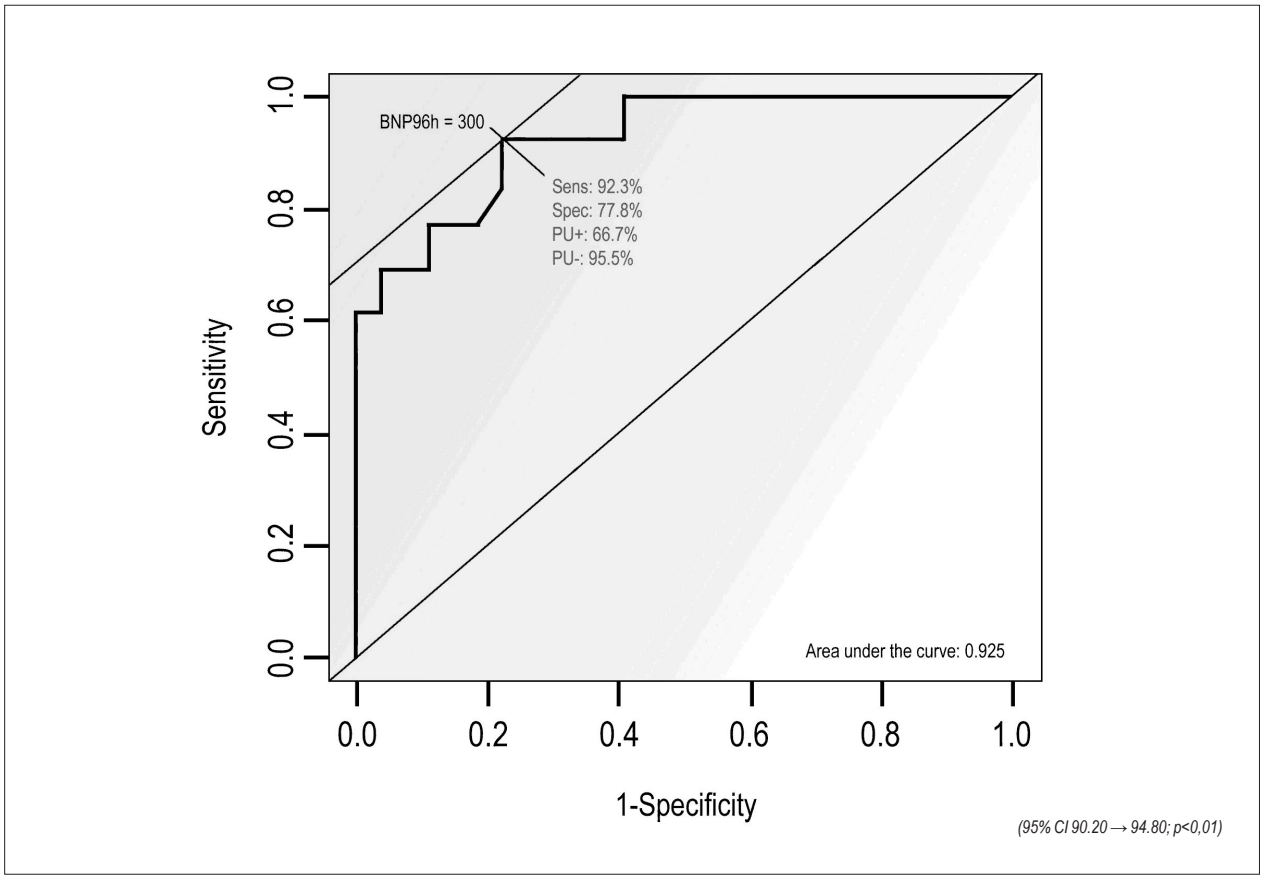

Figure 3 - *ROC curve for the 96-hour BNP during the four-year follow-up*

Table 4 - Logistic regression among age, 96-hour BNP, and outcome

Characteristic	Odds ratio	Upper	Lower	p Value
Ten-year age increases	1.50	0.58	3.85	0.40
BNP (300 pg/ml)	15.19	2.15	103.76	< 0.01

Considering the 96-hour BNP cutoff point of 300pg/ml, Table 4 shows a ten-time greater risk ratio then each ten-year increase in age.

It is worth stressing that the analysis of the accuracy of the BNP on admission could not discriminate a significant cutoff point to estimate the risk of events during the follow-up period. This was not observed in the study by Bassan et al.[12], which used the BNP on admission to distinguish the cutoff point as an early and late mortality predictor. Our hypothesis is that 96-hour BNP can be a marker more compatible with the real world in the long-run, because it is the result of the therapeutic approach. As all patients in this study underwent coronary intervention within the first 24 hours after the ischemic event, at the end of 96 hours, all patients had been treated, that is, their therapeutic strategies had already been defined. However, further studies, mainly with a more significant number of patients, should be conducted to confirm that hypothesis.

Eggers et al.[15] have reported an excellent accuracy of NT pro-BNP measured late in the course of ACS (at six weeks and after six months). Thus, in addition to being death predictors when measured during hospitalization, since natriuretic peptides can indicate the ischemic area, they can also add prognostic information when analyzed after treatment definition.

This study also assessed the possible associations between the TIMI Risk Score and BNP values on admission and 96 hours after that.

A clear association was noted between the 96-hour BNP and a TIMI Risk Score increase. Analyzing the graph of that association (Figure 1), the drop observed can result from the reduced number of individuals with a TIMI Risk Score of 6. We also believe that 96-hour BNP acted as an additional prognostic marker to TIMI Risk Score, which is a well defined risk stratification tool for NSTE-ACS in the short and long run[4]. However, two recently published studies have also shown the greater prognostic value of NT pro-BNP as compared with that of the TIMI Risk Score[16-17].

The literature lacks uniform criteria to quantify myocardial ischemic area in terms of BNP values. The two major studies by Sadanandan et al.[18] and Ndrepepa et al.[19] have used, as the criteria for estimating the myocardial area at risk for ischemia, the effects on the anterior descending coronary artery and the three-vessel anatomy, respectively.

In our case series, the increase in BNP values 96 hours after hospital admission and coronary intervention indicated patients with larger myocardial areas at risk for ischemia and multivessel disease. The electrocardiographic alterations, ST-segment decrease and/or T-wave inversion, and echocardiographic alterations, segmental dysfunction, compatible with myocardial ischemia were more prevalent in the group of patients with multivessel disease (Table 2).

The previous studies have shown that a sharp increase in serum BNP levels during an ischemic event, with no evidence of systolic dysfunction, can be associated with the complexity and severity of the coronary artery anatomy. For example, Sabatine et al.[20] have reported, during transitory myocardial ischemia, a significant increase in serum BNP levels, and the increase was associated with the severity of the ischemic disease.

In our study, a significant increase in BNP level was observed 96 hours after admission ($p=0.02$) in the population with larger myocardial areas at risk for ischemia and multivessel disease. We decided not to use a cutoff point, because we already had BNP levels on admission and after 96 hours; thus, the importance of the increase during the period was assessed.

It is worth noting that, in our case series, the BNP levels found were higher than those reported in the literature. Analyzing some previous studies, we observed that the BNP cutoff point has been modified depending on the purpose of the research project. For diagnosing heart failure, a cutoff point of 200 pg/ml is extremely accurate[21]. In patients with chest pain, BNP >100 pg/ml is a strong predictor of acute myocardial infarction[22]. For patients with NSTE-ACS, BNP serum levels higher than 80 pg/ml could associate with the severity and extension of the myocardial ischemic area[18]. In this study, a 300-pg/ml cutoff point for 96-hour BNP, could be the BNP representing the result of coronary intervention, defined a group of patients with more severe NSTE-ACS and a 7.4-time higher risk of death in the four-year follow-up.

In a recently published study aiming at analyzing the prognosis of patients with NSTE-ACS, an admission BNP cutoff point of 101 pg/ml

discriminated a relative risk of death of 13.0 in the first month and of 5.3 at one year[12].

Another study has reported the association between NT pro-BNP and the outcome of death in a six-year follow-up in patients with ACS and after myocardial revascularization[23].

The 96-hour BNP could be a useful complementary, easily-calibrated tool for risk stratification of ACS patients, particularly at places lacking hemodynamic laboratory facilities, allowing easy recognition of groups at higher risk for late adverse events.

This study suggests that an increased 96-hour BNP level (> 300 pg/ml) is associated with a higher risk of death during the four-year follow-up of patients with NSTE-ACS. This requires closer clinical monitoring for adjusting cardiovascular risk factors. However, the literature still lacks data justifying the use of a treatment strategy based only on the elevation of BNP levels in ACS patients.

It is easy to understand the increase in BNP among ACS patients with myocardial dysfunction, because the increase in left ventricular filling pressure triggers BNP synthesis and release[24-26]. However, the increased risk for a cardiac event in the population with no left ventricular failure suggests the existence of other mechanisms. The diastolic dysfunction secondary to myocardial ischemia might be one of the factors behind the increase in serum BNP levels in ACS[27-28].

The 96-hour BNP must also be interpreted together with hemodynamic and clinical findings, ECG alterations, elevation in myocardial necrosis markers [creatinine kinase (CK) mass, and troponin], presence of segmental alterations on transthoracic echocardiogram, and inflammatory profile by use of PCR measurement.

Limitations of the study

This study has certain limitations. The small size of the sample could result in a selection bias. The criterion chosen to determine the extension of the myocardial area at risk of ischemia, which was lesion of the left main coronary artery and/or its equivalent, used the degree of artery obstruction as the ischemia parameter, rather than functional assessment. However, because of the clinical severity of the group studied, assessment by use of myocardial scintigraphy or cardiac magnetic resonance, which could be harmful to patients, was not performed.

This study was conducted at a private institution in a prosperous district of the city of Rio de Janeiro, with patients of high socioeconomic and cultural levels. Thus, the risk can have been underestimated, because real world conditions, such as access to medical resources and medications that interfere with the course of the disease, were not considered in the analysis.

Conclusions

1. In patients with NSTE-ACS, a BNP level higher than 300 pg/ml 96 hours after the onset of an ischemic event and of a coronary intervention is associated with a 7.44-time higher risk of death in four years.

2. In this study, the greater increase in the BNP level within 96 hours from admission is associated with a greater severity in coronary artery lesion in NSTE-ACS patients. This association could explain the association between 96-hour BNP and the NSTE-ACS event.

3. Our findings suggest that an association between BNP and TIMI Risk Score can exist.

4. The 96-hour BNP can be a useful tool for the cardiologist to establish the long-term prognosis of patients with NSTE-ACS. However, further studies are required to confirm the best time for BNP assessment (be it on admission or after the intervention) during the hospitalization of individuals with NSTE-ACS and positive troponin.

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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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