Prognostic Value of Perioperative N-Terminal Pro-B-Type Natriuretic Peptide in Noncardiac Surgery

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Abstract

Background: Preoperative NT-proBNP has been shown to predict adverse cardiac outcomes, although recent studies suggested that postoperative NT-proBNP determination could provide additional information in patients submitted to noncardiac surgery.

Objective: To evaluate the prognostic value of perioperative NT-proBNP in intermediate and high risk cardiovascular patients undergoing noncardiac surgery.

Methods: This study prospectively enrolled 145 patients aged ≥45 years, with at least one Revised Cardiac Risk Index risk factor and submitted to intermediate or high risk noncardiac surgery. NT-proBNP levels were measured pre- and postoperatively. Short-term cardiac outcome predictors were evaluated by logistic regression models.

Results: During a median follow-up of 29 days, 17 patients (11.7%) experienced major adverse cardiac events (MACE- 14 nonfatal myocardial infarctions, 2 nonfatal cardiac arrests and 3 cardiac deaths). The optimum discriminatory threshold levels for pre- and postoperative NT-proBNP were 917 and 2962 pg/mL, respectively. Pre- and postoperative NT-proBNP (OR 4.7; 95% CI 1.62–13.73; p=0.005 and OR 4.5; 95% CI 1.53-13.16; p=0.006) were significantly associated with MACE. Preoperative NT-proBNP was significantly and independently associated with adverse cardiac events in multivariate regression analysis (adjusted OR 4.2; 95% CI 1.38-12.62; p=0.011).

Conclusion: NT-proBNP is a powerful short-term marker of perioperative cardiovascular events in high risk patients. Postoperative levels were less informative than preoperative levels. A single preoperative NT-proBNP measurement should be considered in the preoperative risk assessment. (Arq Bras Cardiol. 2013;100(6):561-570)

Keywords: Cardiovascular Diseases / blood; Natriuretic Peptide, Brain / blood; Peptide Fragments / blood; Preoperative Care; Risk Assessment; Surgical Procedures, Operative.

Introduction

Clinical risk stratification plays an important role in preoperative evaluation of patients at risk for cardiac events [1]. Nonetheless, this approach is not always sufficient to predict postoperative cardiac complications. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a marker of myocardial dysfunction (ischemic and stretch), and a powerful predictor of major adverse cardiovascular events and death in multiple cardiologic settings [2-4].

Preoperative NT-proBNP elevation has been independently associated with adverse cardiac outcomes after major noncardiac surgeries [5-8], and it is unknown whether postoperative NT-proBNP levels indicate myocardial dysfunction and whether it is a reliable indicator of cardiac stress and outcome. A single postoperative NT-proBNP level could provide additional prognostic information for major cardiac events [9]. NT-proBNP measurement has not yet been incorporated into the routine monitoring of intermediate and high-risk cardiovascular patients undergoing noncardiac surgery [10]; moreover, the value of postoperative NT-proBNP as a marker of in-hospital and short-term cardiac events is still unknown.

Thus, this study aims to evaluate the additional prognostic value of postoperative NT-proBNP in intermediate and high-risk cardiovascular patients undergoing noncardiac surgery after adjusting for clinical factors and preoperative levels.

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Methods

Patients Selection

After Institutional Ethics Review Board approval, all patients scheduled to undergo elective noncardiac surgery between June 2010 and February 2011 were screened for

eligibility for this prospective observational study. Before participating, all patients provided written informed consent and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Patients older than 45 years of age, with one or more Revised Cardiac Risk Index risk factor (history of ischemic heart disease, history of heart failure, insulin-dependent diabetes mellitus, stroke or transient ischemic attack, or renal failure [serum creatinine level > 2 mg/dl, or patients on renal replacement therapy]) and undergoing surgery defined as intermediate or high-risk by the American College of Cardiology/American Heart Association [1] and who had been hospitalized at least one day before surgery were eligible for study inclusion.

The sample size estimated for the cohort study was based on an anticipated rate of combined major adverse vascular events (vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest) of 6% based on previous studies [11,12]. It was expected that approximately 142 patients were to be included, assuming a hazard ratio of four for high NT-proBNP levels, with an 80% power and an alpha error of 5%[7].

Biochemical Markers

Blood samples were collected in serum tubes and centrifuged within 10 minutes. After determination of cardiac troponin I (cTnI), serum was frozen and stored in aliquots at -80°C. NT-proBNP was measured and analyzed after including all patients in the study. Troponin I was determined on postoperative days one and two. The Siemens cTnI Ultra assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens Healthcare Diagnostics-Deerfield, Illinois, United States), with a limit of detection of 0.006 μg/L, a 99th percentile cutoff point of 0.04 μg/L and a coefficient of variation below 10%, at a level of 0.03 μg/L, as specified by the manufacturer.

NT-proBNP levels were determined using the Roche Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany). Serum determinations (electrochemiluminescence sandwich immunoassay, Elecsys ProBNP; Roche Diagnostics) were performed the day before surgery and on postoperative day two. The assay had an analytical sensitivity of 5 pg/ml, and intraassay and interassay coefficients of variance below 3%.

Perioperative Care

Serial 12-lead electrocardiogram recordings were performed postoperatively when cTnI values were greater than 0.04 μg/L or whenever clinically indicated. Standard two-dimensional, M-mode and Doppler echocardiography (Envisor C, iE33; Philips Medical Systems, Andover, United States, Vivid 3 or Vivid 7; GE Healthcare, Milwaukee, United States) was performed by a cardiologist postoperatively, for those patients whose cTnI values were greater than 0.04 μg/L and a nondiagnostic electrocardiogram.

The attending physicians were aware of perioperative echocardiographic data and cTnI levels of patients, but were unaware of the NT-proBNP levels.

Follow-up

Patients were monitored in-hospital and after 30 days for the occurrence of short-term cardiac events. The study primary outcome was defined as combination of vascular death, nonfatal myocardial infarction and nonfatal cardiac arrest after index surgery. A telephone interview conducted by an investigator unaware of NT-proBNP levels was performed in all patients 30 days after index surgery. In case of hospital readmission or death since index surgery, hospital charts and death certificates were reviewed. Vascular complications were documented by the study physicians and validated by two independent investigators. Both data collectors and outcome adjudicators were blinded to measured NT-proBNP levels.

Vascular death was defined as death due to myocardial infarction, stroke, arrhythmia, heart failure or vascular events of great vessels. Nonfatal cardiac arrest was defined as a cardiopulmonary event that led to the initiation of successful cardiopulmonary resuscitation. Nonfatal myocardial infarction was diagnosed by a typical rise and fall of cTnI to greater than 0.04 μg/L, along with clinical signs or symptoms of ischemia or electrocardiographic findings (new Q waves or ST-T wave changes in at least two adjacent leads, or new left bundle branch block) suggestive of acute myocardial ischemia.

Secondary outcome variable was a combined endpoint of death, nonfatal stroke, congestive heart failure, atrial fibrillation and acute coronary revascularization procedures. Stroke was considered as a new focal neurological deficit of vascular origin, with symptoms lasting for more than 24 hours. Diagnosis of congestive heart failure required one or more of the following conditions: development of symptoms or signs of pulmonary edema, evidence of left ventricular failure or some abnormal finding on chest radiography. Atrial fibrillation with hemodynamic compromise was considered significant. Acute coronary revascularization included percutaneous coronary intervention or coronary artery bypass grafting related to persistent myocardial ischemia and hemodynamic compromise refractory to medical therapy.

Statistical Methods

Results are shown as mean and standard deviation (SD), medians and interquartile range [25th-75th percentiles], or absolute and relative frequencies as appropriate. Preoperative NT-proBNP values and their perioperative changes were compared using Mann-Whitney U test. In order to test the strength of the associations between NT-proBNP levels and other continuous variables, Spearman's rank correlation was used. Receiver operating characteristic curves were constructed to assess the diagnostic accuracy of the NT-proBNP levels for the primary outcome. To determine optimal values of specificity and sensitivity, the closest value to the best specificity and sensitivity point on the receiver operating characteristic curve was identified. Sensitivity, specificity, and positive and negative predictive values were calculated. For the purpose of assessing event-free survival, a Kaplan-Meier analysis was performed. The event-time curve was separated according

to the discriminatory pre- and postoperative NT-proBNP levels and these curves were compared by log-rank test. Patients with and without events were compared by univariate analyses using Student's *t* test, Chi-square test, Mann-Whitney U test, or Fisher exact test, as appropriate. Multivariate analysis was performed to determine independent factors associated with cardiac complications. Only clinically relevant variables with $p < 0.20$ in the univariate analysis were included in the multivariable model. The level of significance was a two-tailed p value < 0.05. Statistical analysis was performed using SPSS 18.0 for Windows.

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Results

Between June 2010 and February 2011, all 155 consecutive patients scheduled to undergo intermediate or high-risk noncardiac surgery that met the inclusion criteria were enrolled. Ten patients (6.5%) had their surgeries canceled after enrollment. There was no statistically significant difference between the clinical characteristics of patients who did not undergo surgery, in comparison with those 145 patients included in the study. Baseline characteristics of included patients are shown in Table 1. Perioperative patient characteristics stratified by the occurrence of cardiovascular events during follow-up are shown in Table 2.

During a median follow-up of 29 (8.7) days, 17 patients (11.7%) experienced major adverse cardiac events, including 14 nonfatal myocardial infarctions (9.7%), two nonfatal cardiac arrests (1.4%) and three cardiac deaths (2.1%). Overall mortality (cardiac and noncardiac) was 6.9%, including four cases of sepsis, three cases of hemorrhagic shock and three cases of cardiovascular deaths.

Forty-seven patients (32.4%) had cTnI elevation (≥0.04 μg/L) in at least one of the postoperative samples collected. Among these, 14 patients had a diagnosis of acute myocardial infarction. Echocardiography was performed postoperatively in all but two patients with cTnI ≥0.04 μg/L and a nondiagnostic electrocardiogram.

Association of perioperative NT-proBNP and cardiovascular events

Median NT-proBNP has significantly increased from 332 to 1175 pg/mL (interquartile range, 115-1743 to 587-2987 pg/mL; $p<0.001$), before and after surgery, respectively. Overall, 109 patients (78%) had an increase in NT-proBNP after surgery. Preoperatively, median NT-proBNP levels were higher in patients who experienced postoperative major adverse cardiac events as compared with event-free patients (1730 vs. 288 pg/mL; $p=0.02$). In addition, the median postoperative NT-proBNP was greater in patients experiencing major adverse cardiac events when compared with event-free patients (3699 vs. 1092 pg/mL; $p=0.01$; Figure 1). Pre- and postoperative NT-proBNP levels were strongly correlated ($r=0.74$; $p<0.001$). Postoperative cTnI levels were moderately correlated with pre- and postoperative NT-proBNP levels ($r=0.43$; $p<0.001$, and $r=0.40$; $p<0.001$, respectively).

The association between perioperative NT-proBNP and major adverse cardiac events was assessed by means of a receiver operating characteristic curve (Figure 2). The area under the curve was 0.67 (95% CI 0.52-0.82) for preoperative NT-proBNP. The optimum discriminate threshold for preoperative NT-proBNP was 917 pg/mL, yielding a sensitivity of 65%, a specificity of 73%, a positive predictive value of 24%, and a negative predictive value of 94%. For postoperative NT-proBNP, the area under the curve was 0.69 (95% CI 0.54-0.84). A discriminative threshold of 2962 pg/mL had the best combined sensitivity (56.3%) and specificity (78%) rates, a positive predictive value of 24.3%, and a negative predictive value of 93.3%. Models including the Revised Cardiac Risk Index were characterized by a low discriminative power (c-index=0.61±0.08) in predicting major adverse cardiac events. The c-index increased to 0.65±0.08 ($p=0.39$), 0.64±0.08 ($p=0.31$), and 0.65±0.08 ($p=0.16$) when preoperative, postoperative, and both NT-proBNP levels were included, respectively. The association of pre- and postoperative NT-proBNP and cardiovascular events is shown in Tables 3 and 4.

Figure 3 shows the Kaplan-Meier curve demonstrating event-free survival in patients with NT-proBNP levels less than and greater than the established threshold. When comparing by log-rank test, the combination of both pre- and postoperative NT-proBNP levels – under or above the optimum discriminate threshold – of patients with both negative results showed higher event-free survival rates than those with both positive results ($p<0.001$) during the 30-day postoperative follow-up period (Figure 3C).

Multivariate analysis

Previous percutaneous coronary intervention, peripheral artery disease, Specific Activity Scale class, vascular surgery, postoperative cTnI, major transoperative bleeding, pre- and postoperative NT-proBNP were significantly associated with major adverse cardiac events in univariate analysis (Tables 1 and 2). Adjusted for Revised Cardiac Risk Index, coronary revascularization, preoperative use of beta-blockers, vascular surgery and preoperative NT-proBNP levels by logistic regression, postoperative NT-proBNP levels were no longer associated with adverse cardiac events. In multivariate regression analysis, independent predictors of major adverse cardiac events were preoperative NT-proBNP level ≥ 917 pg/mL (OR 4.2; 95% CI: 1.38-12.62; $p=0.011$) and vascular surgery (OR 3.2; 95% CI: 1.06-9.53; $p=0.04$). Relative and absolute variations of NT-proBNP from preoperative to postoperative levels were not significantly associated with postoperative cardiac events in the study population.

When stratifying patients by Revised Cardiac Risk Index and pre- and postoperative NT-proBNP levels, the primary outcome was similar among patients in class II and III. Class IV patients and pre- or postoperative NT-proBNP levels below the optimum discriminatory threshold levels showed lower event rates than those with class IV and pre- or

Table 1 - **Baseline characteristics for the entire cohort and for patients with and without 30-day cardiovascular events; data are expressed as mean ± SD, number (proportion) or median [interquartile range] as appropriate**

	All patients (n=145)	Cardiovascular events		p
		Yes (n=17)	No (n= 128)	
Men	70 (48.3)	8 (47)	62 (48.4)	1.00
Age, years	65.7±9.8	64.8±10.8	65.8±9.7	0.67
ASA scoring system				0.35
Class II	53 (36.6)	4 (23.5)	49 (38.2)	
Class III	86 (59.3)	13 (76.5)	73 (57)	
Class IV	6 (4.1)	0	6 (4.7)	
Specific Activity Scale*				**0.01**
Class I	49 (33.8)	4 (23.5)	45 (35.1)	
Class II	41 (28.3)	3 (17.6)	38 (29.7)	
Class III	33 (22.8)	2 (11.8)	31 (24.2)	
Class IV	13 (9)	6 (35.3)	7 (5.5)	
Revised Cardiac Risk Index				0.19
Class II	13 (9)	1 (5.9)	12 (9.4)	
Class III	85 (58.6)	8 (47)	77 (60.1)	
Class IV	47 (32.4)	8 (47)	39 (30.5)	
Current smokers	33 (22.8)	4 (23.5)	29 (22.6)	0.89
Diabetes mellitus	60 (41.4)	8 (47)	52 (40.6)	0.61
Atrial fibrillation	13 (9)	2 (11.7)	11 (8.6)	0.65
History of congestive heart failure	26 (17.9)	5 (29.4)	21 (16.4)	0.19
LVEF (%)†	61.5 ±10.1	57 ±12	62 ±9.5	0.06
Hypertension	125 (86.2)	15 (88.2)	110 (85.9)	1.00
History of myocardial infarction	49(33.8)	7 (41.2)	42 (32.8)	0.58
Previous PCI‡	24 (16.6)	6 (35.3)	18 (14.1)	0.04
Previous CABG§	17 (11.7)	4 (23.5)	13 (10.1)	0.11
History of cerebrovascular disease	47 (32.4)	6 (35.3)	41 (32.0)	0.78
Renal impairment//	36 (24.8)	5 (29.4)	31 (24.2)	0.76
Peripheral artery disease	30 (20.7)	9 (52.9)	21 (16.4)	0.002
Preoperative laboratory tests				
Hemoglobin, mg/dl	11.8±2.3	11.5±2.6	11.8±2.2	0.53
Serum creatinine, mg/dl	1.11 [0.86-1.75]	1.34 [0.91 - 2.87]	1.09 [0.86 -1.72]	0.35
Creatinine clearance, ml/min	58.6±31.48	55.95±41.17	58.94±30.22	0.78
NT-proBNP, pg/ml¶	331.6 [115-1743]	1730 [2234-9929]	288 [104 -1332]	0.02
Preoperative medication				
Aspirin	66 (45.5)	9 (52.9)	57 (44.5)	0.6
Clopidogrel	11 (7.6)	1 (5.9)	10 (7.8)	1.00
Insulin	33 (22.8)	7 (41.2)	26 (20.3)	0.07
Statins	76 (52.4)	9 (52.9)	67 (52.3)	1.00
β-Blockes	73(50.3)	12 (70.6)	61 (47.6)	0.12
ACE inhibitors#	86 (59.3)	10 (58.8)	76 (59.4)	1.00

**n=136; †LVFE- Left ventricular ejection fraction n=116; ‡PCI- percutaneous coronary intervention; §CABG- coronary artery bypass graft; //Serum creatinine ≥2.0 mg/dl or renal replacement therapy; ¶NT-proBNP- N-terminal pro-B-type natriuretic peptide n=142; #ACE- angiotensin-converting enzyme*

Table 2 - **Perioperative characteristics of all patients, stratified by the occurrence of 30-day cardiovascular events; data are expressed as number (proportion) or median [interquartile range] as appropriate**

	All patients (n=145)	Cardiovascular events		p
		Yes (n=17)	No (n=128)	
Postoperative laboratory tests				
NT-proBNP, pg/ml*	1175 [587-2987]	3699 [926 -12989]	1091.5 [558 -2759]	0.01
cTnI postoperative day 1, µg/L†	0.018 [0.009-0.036]	0.049 [0.02 -0.425]	0.017 [0.008-0.032]	0.001
cTnI postoperative day 2, µg/L‡	0.019 [0.01-0.053]	0.192 [0.059-0.686]	0.018 [0.009-0.034]	< 0.001
Transoperative events				
Hypotension (Systolic < 100 mmHg)	93 (64.1)	10 (58.8)	83 (64.8)	0.6
Bradycardia (Heart rate < 50 bpm)	33 (22.8)	4 (23.5)	29 (22.6)	1.00
Major bleeding§	19 (13.1)	6 (35.3)	13 (10.1)	0.01
Types of surgery				**0.03**
Abdominal	72 (49.7)	4 (23.5)	68 (53.1)	
Thoracic	10 (6.9)	0	10 (7.8)	
Vascular	46 (31.7)	10 (58.8)	36 (28.1)	
Prostate	4 (2.8)	0	4 (3.1)	
Hip	13 (9)	3 (17.6)	10 (7.8)	

** NT-proBNP: N-terminal pro-B-type natriuretic peptide n=142; †cTnI- cardiac troponin I; n=141; ‡n=138; §Major bleeding- bleeding requiring blood transfusion.*

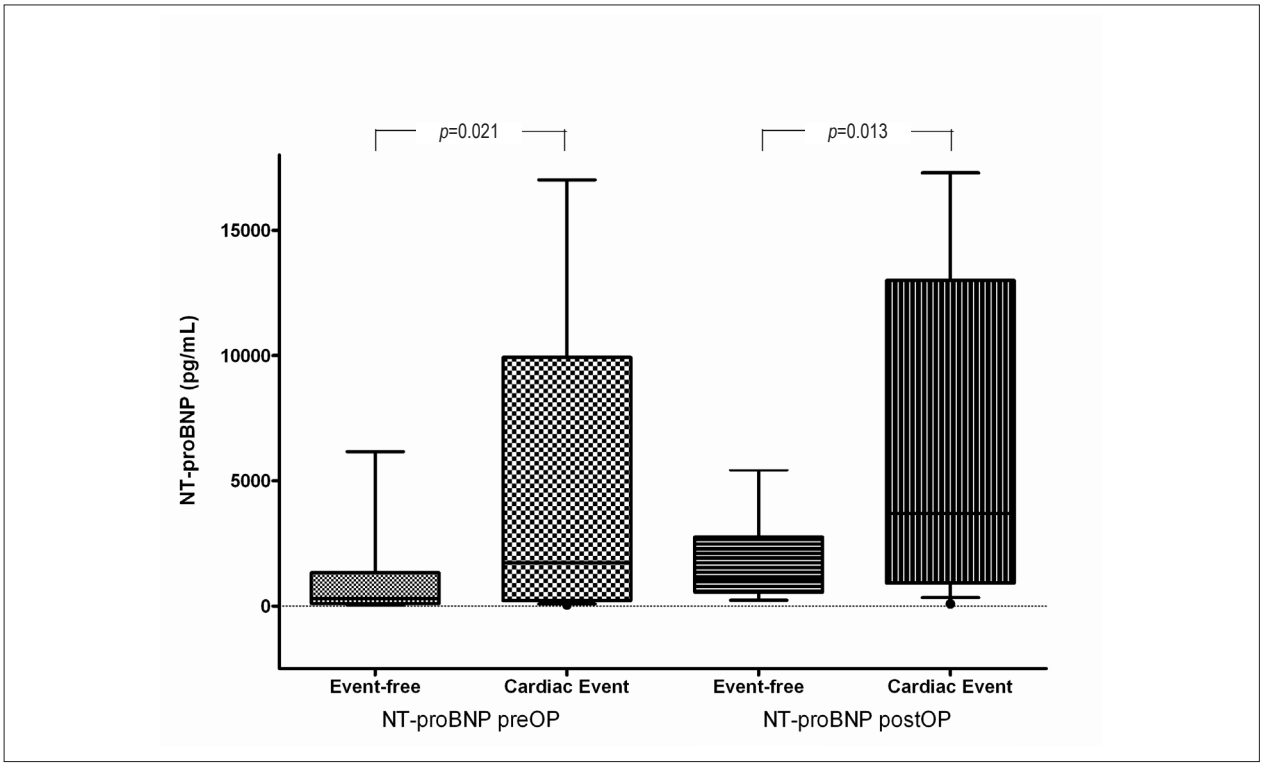

Figure 1 - *Box-and-whisker plots of preoperative (preOP) and postoperative (postOP) N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in patients with and without cardiac events after index surgery.*

postoperative NT-proBNP above the threshold levels during the 30-day postoperative follow-up period (p=0.004 and p=0.002, respectively).

Discussion

This study demonstrates that perioperative NT-proBNP measurement provides valuable information for risk stratification of intermediate and high-risk patients undergoing noncardiac surgery. Preoperative NT-proBNP level higher than 917 pg/mL resulted in a four-fold increase in the odds for major adverse cardiac events in a short-term period. Patients with both pre- and postoperative NT-proBNP levels under the optimum discriminatory threshold had higher event-free survival rates when compared with those with both positive results during the 30-day postoperative follow-up period. Yet, after adjustment for preoperative clinical variables, the most independent predictor of primary cardiac events was preoperative NT-proBNP level.

This study confirms and extends previous findings on preoperative NT-proBNP as an independent marker associated with major cardiovascular events [9,13-18]. In contrast, the value of postoperative NT-proBNP determination in this clinical setting remains undefined. As observed in this study, NT-proBNP levels vary substantially during the postoperative period[7,9,18-22]. Postoperative peptide levels may reflect the variable dynamic consequences of anesthesia exerted by intraoperative and postoperative catecholamine release and induced hypercoagulability, which could precipitate postoperative ischemia, myocardial infarction and cardiac dysfunction after major surgeries.

Few studies were designed to address diagnostic and prognostic values of postoperative NT-proBNP for adverse cardiac outcomes. Prior studies limited to vascular patients have found discordant results [9,23,24]. Mahla et al[9] have assessed 218 patients undergoing elective major vascular surgery and identified a greater rise in postoperative NT-proBNP in those patients who sustained cardiovascular events, in comparison with those who did not (609 vs. 183 pg/mL). The authors concluded that a single postoperative NT-proBNP ≥ 860 pg/mL could provide incremental prognostic information compared to preoperative levels (in-hospital adjusted hazard ratio 19.8; 95% CI: 3.4-115)[9]. In a cohort study involving 144 vascular patients, Goei et al. have demonstrated that the difference in NT-proBNP levels between pre- and postoperative measurements was the strongest independent predictor of long-term cardiac outcome (adjusted hazard ratio of 3.06; 95% CI: 1.36-6.91)[23]. Similar to findings by Rajagopalan et al., postoperative NT-proBNP was an independent predictor of mortality among vascular patients, but not of major adverse cardiac events [24].

Results from our cohort demonstrate that, in spite of the substantial postoperative NT-proBNP increase, only preoperative measurements remained statistically significant in multivariate analysis. One might consider reasons for these different findings. Firstly, former studies have evaluated populations at higher risk and included older patients submitted to vascular surgery only. Secondly, NT-proBNP was measured latter in the postoperative period, which could eliminate possible confounders, as patients were usually no longer receiving infusion therapies. Thirdly, and probably more relevant, studies usually failed to adjust for preoperative

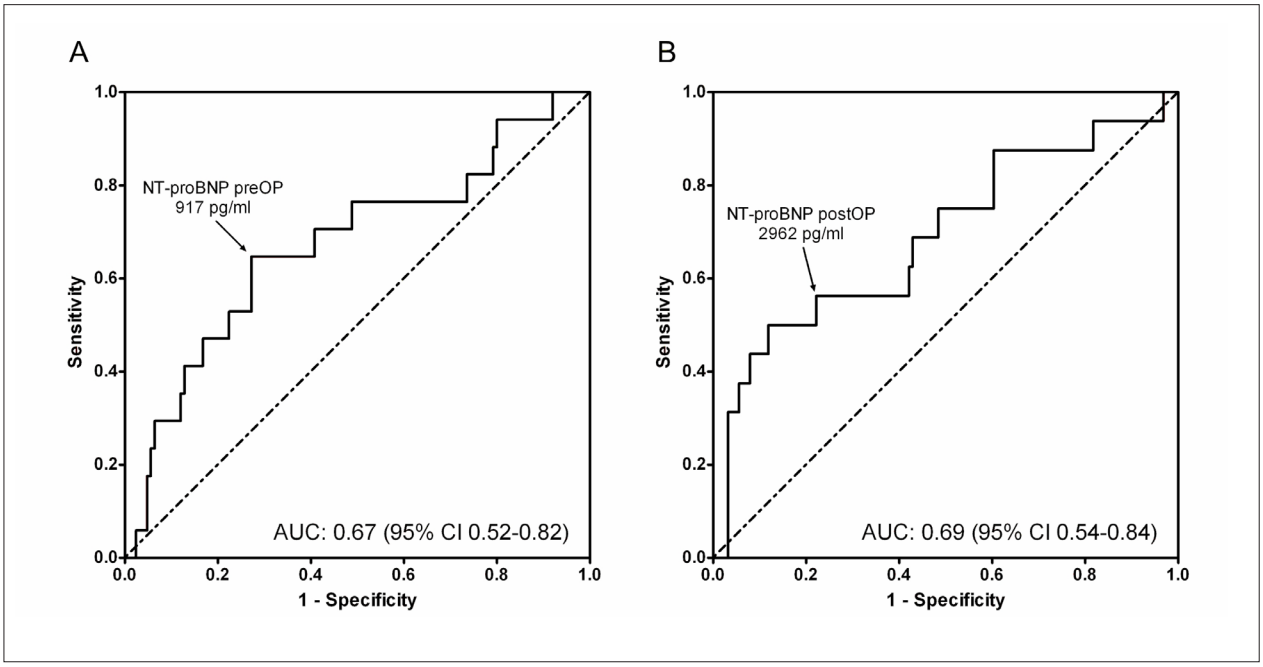

Figure 2 - *Receiver operating characteristic (ROC) curves for preoperative (preOP) (A) and postoperative (postOP) (B) N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels for the prediction of the combined endpoint of vascular death, nonfatal myocardial infarction or nonfatal cardiac arrest after index surgery. AUC = area under the curve; CI = confidence interval.*

Table 3 – **Events during follow-up period, stratified by preoperative N-terminal pro-B-type natriuretic peptide**

	All patients n=145 (%)	NT-proBNP* <917 pg/ml n=96 (%)	NT-proBNP* ≥917 pg/ml n=46 (%)	OR (95% CI)
Primary outcome	17 (11.7)	6 (6.3)	11 (23.9)	4.71 (1.62 – 13.73)
Cardiac death	3 (2.1)	0	3 (6.5)	14.6 (0.7 – 275)‡
Nonfatal cardiac arrest	2 (1.4)	0	2 (4.3)	10.84 (0.52 –226.29)‡
Nonfatal myocardial infarction	14 (9.7)	6 (6.3)	8 (17.4)	3.16 (1.03 – 9.72)
Secondary outcome	29 (20)	13 (13.5)	15 (32.6)	3.09 (1.32 – 7.23)
Death	10 (6.9)	2 (2.1)	7 (15.2)	8.43 (1.67 – 42.42)
Nonfatal stroke	5 (3.4)	3 (3.1)	2 (4.3)	1.41 (0.23 –8.74)
Congestive heart failure	12 (8.3)	8 (8.3)	4 (8.7)	1.05 (0.30 – 3.68)
Atrial fibrillation	7 (4.8)	1 (1.0)	6 (13)	14.25 (1.66 – 122.21)
Coronary revascularization	1 (0.7)	1 (1.0)	0	0.68 (0.03 – 16.62) ‡
Noncardiovascular outcome†	59 (40.7)	33 (34.4)	25 (54.3)	2.27 (1.11-4.65)
Noncardiac death	7 (4.8)	2 (2.1)	4 (8.7)	4.47 (0.79 – 25.4)
Infection	43 (29.7)	22 (23)	21 (45.7)	2.82(1.33 – 5.98)
Renal failure	7 (4.8)	2 (2.1)	4 (8.7)	4.47 (0.79 – 25.4)
Major bleeding	37 (25.5)	19 (19.8)	17 (37)	2.37 (1.09 – 5.19)

**NT-proBNP: N-terminal pro-B-type natriuretic peptide; †Combined outcome of noncardiovascular events: noncardiac death, infection, acute renal insufficiency with necessity of renal replacement therapy or postoperative major bleeding (bleeding requiring blood transfusion); ‡Adjusted by adding 0.5 in each cell, if there is a zero frequency.*

Table 4 - **Events during follow-up period, stratified by postoperative N-terminal pro-B-type natriuretic peptide**

	All patients n=145 (%)	NT-proBNP* < 2962 pg/ml n=105 (%)	NT-proBNP* ≥ 2962 pg/ml n=37 (%)	OR (95% CI)
Primary outcome	17 (11.7)	7 (6.7)	9 (24.3)	4.5 (1.53 – 13.16)
Cardiac death	3 (2.1)	0	2 (5.4)	14.86 (0.71 – 310.96)‡
Nonfatal cardiac arrest	2 (1.4)	0	2 (5.4)	14.86 (0.71 – 310.96)‡
Nonfatal myocardial infarction	14 (9.7)	7 (6.7)	7 (18.9)	3.26 (1.06 – 10.05)
Secondary outcome	29 (20)	18 (17.1)	10 (27)	1.79 (0.73 – 4.33)
Death	10 (6.9)	4 (3.8)	5 (13.5)	3.94 (1 – 15.58)
Nonfatal stroke	5 (3.4)	5 (4.8)	0	0.24 (0.01 – 4.35)‡
Congestive heart failure	12 (8.3)	9 (8.6)	3 (8.1)	0.94 (0.24 – 3.68)
Atrial fibrillation	7 (4.8)	3 (2.9)	4 (10.8)	4.12 (0.87- 19.37)
Coronary revascularization	1 (0.7)	1 (1.0)	0	0.93 (0.04 – 22.48)‡
Noncardiovascular outcome†	59 (40.7)	37 (35.2)	21 (56.8)	2.41 (1.12 – 5.17)
Noncardiac death	7 (4.8)	4 (3.8)	3 (8.1)	2.23 (0.47 – 10.5)
Infection	43 (29.7)	25 (23.8)	17 (46)	2.72 (1.24 – 5.98)
Renal failure	7 (4.8)	3 (2.9)	4 (10.8)	4.12 (0.88 – 19.4)
Major bleeding	37 (25.5)	23 (22)	13 (35)	1.93 (0.85- 4.38)

**NT-proBNP- N-terminal pro-B-type natriuretic peptide; †Combined outcome of noncardiovascular events: noncardiac death, infection, acute renal insufficiency with necessity of renal replacement therapy or postoperative major bleeding (bleeding requiring blood transfusion); ‡Adjusted by adding 0.5 in each cell, if there is a zero frequency.*

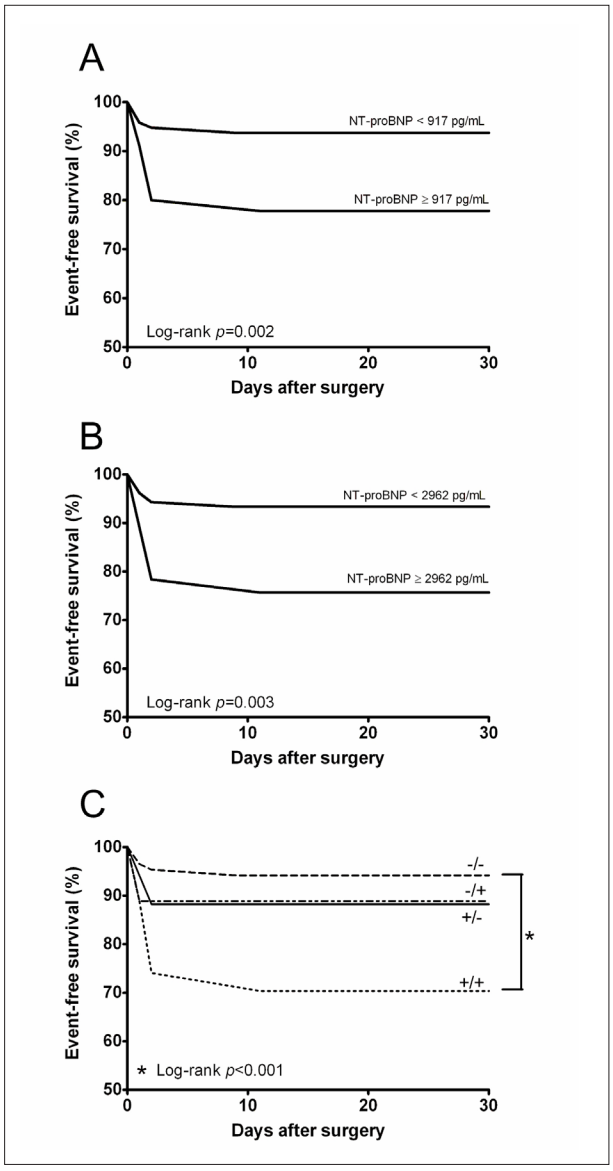

Figure 3 - *Kaplan Meier event-free survival stratified by preoperative N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (A), postoperative NT-proBNP levels (B) and combination of both pre- and postoperative NT-proBNP levels (C), respectively, under (-) or above (+) the optimum discriminate threshold during the 30-days postoperative follow-up period.*

NT-proBNP level, which is the most evident confounder of increased postoperative NT-proBNP level [7].

Data from this study have demonstrated that preoperative NT-proBNP measurements have a useful role, regardless of the Revised Cardiac Risk Index prediction in this setting. This finding suggests that high baseline NT-proBNP levels resulting from the activation of the cardiac neurohormonal system may be a unifying feature in patients at high risk for cardiovascular mortality or major adverse cardiac events. A postoperative level reflects the dynamic consequences of surgery and anesthesia, but the most important factor predicting postoperative cardiovascular outcomes seems to be patients' baseline condition.

In agreement with our results, evidence strongly suggests that there is an independent association between elevated preoperative NT-proBNP levels and increased risks of adverse perioperative cardiovascular outcomes [7,9,13-18,25-30], although risks vary widely among studies and there is uncertainty regarding the strength of the association. A recently published systematic review and meta-analysis intended to determine whether preoperative B-type natriuretic peptide (BNP) or NT-proBNP were independent predictors of 30-day adverse cardiovascular outcomes after noncardiac surgery has included nine studies and a total of 3,281 patients. All studies included showed a statistically significant association between elevated preoperative BNP or NT-proBNP levels and several cardiovascular outcomes. Data pooled from seven studies have demonstrated an odds ratio of 19.3 (95% CI 8.5-43.7; $I^2 = 58\%$)[6]. Yet, there has been a marked heterogeneity across study results.

In addition, no cutoff has been established for risk definition. Previous studies have used different thresholds, from 201 to 1619 pg/mL [9,15-18,21], for preoperative NT-proBNP assays, and from 625 to 860 pg/mL [9,24], for postoperative NT-proBNP assays to represent abnormal values. The cutoff point based on the closest value to the best specificity and sensitivity point on the receiver operating characteristic curve in relation to the primary outcome was 917 pg/mL for preoperative NT-proBNP, and 2962 pg/mL, for postoperative levels. In contrast to other cohorts[9,24], 25% of patients with renal failure were included in this study. NT-proBNP levels and its prognostic ability could be affected by renal failure [31], although it is important to point out that patients with progressive renal failure would have cardiovascular dysfunction coupled to their degree of renal function, which in turn could result in higher NT-proBNP levels [32]. Moreover, the timing used for measurement of pre- and postoperative NT-proBNP levels varies between studies. It is unlikely that there is a dichotomous threshold that defines a normal or abnormal NT-proBNP value. It is more presumable that perioperative cardiovascular risks increase as NT-proBNP concentrations increase.

The use of biochemical tests for risk stratification has several advantages. It only requires a single blood test; which is widely available on existing clinical biochemistry analyzers and is routinely performed in many hospitals. In addition, it could avoid the difficulties of using complex scoring systems in individual patients and also provides an objective measurement, without the risk of potential subjective interpretation of clinical parameters. A clearly defined cutoff point, such as the 917 pg/mL derived from the receiver operating characteristic curve analysis used in this study would be simple to use in a clinical setting. It is a seemingly fast and cost-effective method to enhance preoperative cardiovascular risk assessment and facilitate targeted interventions that may reduce morbidity and mortality.

This study has some caveats. The small number of some events may have resulted in unreliable associations. Nevertheless, a consistent outcome has been evaluated and the adjusted odds were statistically significant. Multivariate models were not adjusted for functional class, given that it was not possible to evaluate functional capacity of most patients limited by peripheral artery disease. Most events occurred in the first days after surgery, and it is possible that elevated postoperative NT-proBNP levels are a consequence instead of predictors of these events. Furthermore, the findings may not be applicable to low-risk patients and to the emergency surgery setting.

Conclusions

Postoperative NT-proBNP determination has a significant association with perioperative major adverse cardiac events, but its additional value to preoperative levels in risk stratification of patients undergoing noncardiac surgery was not confirmed. A single preoperative measurement of NT-proBNP has an independent association with consistent short-term cardiovascular events and could provide further prognostic information to the current strategies used to estimate perioperative risk predictions.

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Author contributions

Conception and design of the research: Borges FK, Furtado MV, Rossini APW, Bertoluci C, Gonzalez VL, Grutcki DM, Rech LG, Magalhães M, Polanczyk CA; Acquisition of data: Borges FK, Furtado MV, Rossini APW, Bertoluci C, Gonzalez VL, Bertoldi EG, Grutcki DM, Rech LG, Magalhães M; Analysis and interpretation of the data: Borges FK, Furtado MV, Rossini APW, Bertoluci C, Gonzalez VL, Bertoldi EG, Grutcki DM, Rech LG, Magalhães M, Polanczyk CA; Statistical analysis: Borges FK, Furtado MV, Gonzalez VL, Polanczyk CA; Obtaining funding: Borges FK, Polanczyk CA; Writing of the manuscript: Borges FK, Furtado MV, Bertoldi EG, Polanczyk CA; Critical revision of the manuscript for intellectual content: Borges FK, Polanczyk CA.

Potential Conflict of Interest

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

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