Association of Plasma N-Terminal Pro-B-Type Natriuretic Peptide With Postoperative Cardiac Events in Patients Undergoing Surgery for Abdominal Aortic Aneurysm or Leg Bypass

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Postoperative cardiac events are related to myocardial ischemia and reduced left ventricular function. The utility of N-terminal–pro-B-type natriuretic peptide (NT–pro-BNP) for preoperative cardiac risk evaluation has not been evaluated. The objective of this study was to assess whether plasma NT–pro-BNP predicts postoperative cardiac events in patients who undergo major vascular surgery in addition to clinical and dobutamine stress echocardiographic data. One hundred seventy consecutive patients scheduled for major noncardiac vascular surgery were prospectively evaluated by dobutamine stress echocardiographic and NT–pro-BNP measurements. Multivariable logistic regression analysis was performed to evaluate the predictors of cardiac death and nonfatal myocardial infarction during a follow-up of 30-days. Receiver-operating characteristic analysis was performed to determine the optimal cut-off value of NT–pro-BNP to predict outcome. Patients' mean age was 59 ± 13 years, and 71% were men. The median NT–pro-BNP level was 110 pg/ml (interquartile range 42 to 389). Cardiac events occurred in 2 of 144 patients (1.4%) with NT–pro-BNP <533 pg/ml (i.e., the optimal cut-off value to predict cardiac events) and in 11 of 26 patients (42%) with NT–pro-BNP ≥533 pg/ml (unadjusted odds ratio 52, 95% confidence interval 11 to 256, p <0.0001). After adjustment for cardiac risk factors and dobutamine stress echocardiographic results, NT–pro-BNP remained significantly associated with cardiac events (adjusted odds ratio 17, 95% confidence interval 3 to 106, p = 0.002). In conclusion, in patients scheduled for major vascular surgery, elevated plasma NT–pro-BNP levels are independently associated with an increased risk for postoperative cardiac events. Further studies in a larger number of patients are required to confirm these findings.
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Patients who undergo major vascular surgery are at increased risk for postoperative cardiac complications due to coronary heart disease.[1,2] To identify high-risk patients before surgery, cardiac risk scores, such as the revised cardiac risk index of Lee et al,[3] are commonly used. In patients with multiple risk factors who undergo high-risk surgery, additional noninvasive stress testing is recommended according to the guidelines of the American Heart Association and the American College of Cardiology.[4] Stress-induced myocardial ischemia and reduced left ventricular function are major determinants of cardiac events in these patients. The aim of this study was to assess the value of N-terminal–pro-B-type natriuretic peptide (NT–pro-BNP) for predicting postoperative cardiac events, in addition to clinical data and dobutamine stress echocardiographic (DSE) results.

Methods

Study population: Patients scheduled for major noncardiac vascular surgery at Erasmus University Medical Center in Rotterdam, The Netherlands, were prospectively included in the study from October 2003 to December 2004 after giving informed consent. The study protocol was approved by the hospital's medical ethics committee. Clinical data were collected by structured interview with patients and by reviewing medical records. On the basis of the revised cardiac risk index of Lee et al,[3] a preoperative cardiac risk score was calculated by assigning 1 point to each of the following cardiac risk factors: high-risk type of surgery, coronary artery disease (angina pectoris or previous myocardial infarction), history of congestive heart failure (mean time of heart failure before surgery 3.5 ± 2 years), history of cerebrovascular disease, insulin therapy for diabetes mel-

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litus, and renal dysfunction (defined as a preoperative serum creatinine level >2.0 mg/dl [177 μmol/L]).[3]

Dobutamine stress echocardiography: Patients underwent 2-dimensional precordial echocardiographic examinations at rest. Standard apical and parasternal views were recorded on videotape, and 12-lead electrocardiograms were recorded. Dobutamine hydrochloride was then administered intravenously by infusion pump, starting at 10 μg/kg/min for 3 minutes (5 μg/kg/min for 5 minutes, followed by 10 μg/kg/min for 5 minutes in patients with wall motion abnormalities at rest) and increasing by 10 μg/kg/min every 3 minutes to a maximum of 40 μg/kg/min. The dobutamine infusion was discontinued if the target heart rate (85% of the theoretic maximal heart rate) was achieved. If the target heart rate was not achieved and patients had no symptoms or signs of ischemia, atropine sulfate (starting at 0.25 mg and increased to a maximum of 2.0 mg) was given intravenously while the administration of dobutamine was continued. Metoprolol was administered (1.0 to 5.0 mg intravenously) to reverse the side effects of the administration of dobutamine or the dobutamine-atropine combination if the side effects did not revert spontaneously and quickly. Two experienced investigators, blinded to the clinical data, performed off-line assessments of echocardiographic images. The left ventricle was divided into 17 segments, and wall motion was scored on a 5-point scale (1 = normal, 2 = mild hypokinesia, 3 = severe hypokinesia, 4 = akinesia, and 5 = dyskinesia). Ischemia was defined as new or worsening wall motion abnormalities (compared with images at rest of the same test), as indicated by an increase in the regional wall motion score of ≥1 grade with stress. Akinesia becoming dyskinesia was not considered an ischemic response.

Measurement of plasma NT–pro-BNP: The mean time of venous blood sampling before surgery was 21 ± 11 days, and all samples were collected before dobutamine stress echocardiography. The samples were centrifuged, and plasma was frozen at −80°C until assay. NT–pro-BNP was measured with an electrochemiluminescence immunoassay kit (Elecsys 2010, Roche Diagnostics GmbH, Mannheim, Germany). The method is a "sandwich"-type quantitative immunoassay based on polyclonal antibodies against epitopes in the N-terminal part of pro-BNP. The lower detection limit was 5 pg/ml. Intra-assay coefficients of variance at 271 and 6,436 pg/ml were 1.9% and 0.9%, respectively. Assays were performed by a laboratory technician blinded to the patients' clinical data.[5]

Outcomes: Patients were monitored for cardiac events for 30 days after surgery. Twelve-lead electrocardiography, serum creatine kinase (CK) measurements (with the MB fraction), and troponin T measurements were performed immediately before surgery and 1, 3, and 7 days after surgery and before discharge. Serum CK and CK-MB activity was measured, and troponin T was measured in heparinized plasma using a chemiluminescence immunoassay. Cardiac death was defined as death caused by acute myocardial infarction, cardiac arrhythmia, or congestive heart failure. Nonfatal myocardial infarction was diagnosed when ≥2 of the following were present: elevated cardiac enzyme levels (CK level >190 U/L and CK-MB >14 U/L, CK-MB fraction >10% of total CK, or cardiac troponin T >0.1 ng/ml), the development of typical electrocardiographic changes (new Q waves >1 mm or >30 ms), and typical symptoms of angina pectoris.

Statistical analysis: Continuous data with a normal distribution are expressed as means and were compared using Student's *t* test. Continuous data with a significant skewed distribution are expressed as medians and were compared using the Mann-Whitney U-statistic test. Categorical data are presented as percentage frequencies, and differences between proportions were compared using the chi-square test with Yates' correction. NT–pro-BNP levels in patients with different DSE results and different cardiac risk scores were compared for trend across ordered groups using analysis of variance techniques. Receiver-operating characteristic curve analysis was performed to calculate sensitivity, specificity, and area under the curve and to select an optimal cut-off value for predicting postoperative cardiac events. Univariate logistic regression analysis was used to evaluate the association of baseline characteristics, DSE results, and NT–pro-BNP values with postoperative outcome. NT–pro-BNP level (dichotomized according to the optimal cut-off value), new wall motion abnormalities (a marker of ischemic heart disease), wall motion abnormalities at rest (a marker of left ventricular dysfunction), renal failure, and diabetes mellitus were analyzed in a final multivariate logistic model. Odds ratios are given with 95% confidence intervals. For all tests, a p value <0.05 (2 sided) was considered significant. All analyses were performed using SPSS version 11.0 statistical software (SPSS, Inc., Chicago, Illinois).

Results

Patient characteristics: The study population consisted of 170 consecutive patients (71% men). The mean age was 59 ± 13 years. Abdominal aortic repair was performed in 67 patients (39%) and lower extremity revascularization in 103 patients (61%). Sixteen patients (9%) had a history of coronary artery revascularization. No patient underwent myocardial revascularization before surgery as a consequence of DSE results. The median concentration of NT–pro-BNP was 110 pg/ml (interquartile range 42 to 389). The baseline characteristics of the patients, subdivided according to a NT–pro-BNP level of 533 pg/ml, are listed in Table 1. Patients with NT–pro-BNP levels ≥533 pg/ml were older and had a greater incidence of angina pectoris, previous myocardial infarction, congestive heart failure, diabetes mellitus, and renal failure compared with patients with NT–pro-BNP levels <533 pg/ml. Q-wave and ST-segment

Table 1
Overall characteristics of patients with elevated plasma N-terminal–pro-B-type natriuretic peptide levels and those with equal or lower levels than the median

Characteristic	NT–pro-BNP (pg/ml)		p Value
	<533 (n = 144)	≥533 (n = 26)	
Age (yrs) (mean ± SD)	59 ± 13	64 ± 11	0.03
Men	98 (68%)	22 (85%)	0.1
Angina pectoris	28 (19%)	17 (65%)	<0.001
Previous myocardial infarction	48 (33%)	21 (81%)	<0.001
Congestive heart failure	25 (17%)	14 (54%)	<0.001
Previous cerebrovascular event	10 (7%)	5 (19%)	0.1
Previous coronary revascularization	14 (10%)	2 (8%)	1.0
Hypertension	35 (24%)	11 (42%)	0.1
Diabetes mellitus	20 (14%)	11 (42%)	0.001
Hypercholesterolemia	57 (40%)	13 (50%)	0.4
Current smoking	25 (17%)	7 (27%)	0.4
Renal failure	0	6 (23%)	<0.001
Aspirin	46 (32%)	10 (38%)	0.7
Angiotensin-converting enzyme inhibitor	48 (33%)	15 (58%)	0.03
β blocker	86 (60%)	23 (88%)	0.01
Calcium channel blocker	19 (13%)	9 (35%)	0.02
Warfarin	23 (16%)	13 (50%)	<0.001
Digoxin	9 (6%)	6 (23%)	0.02
Diuretic	33 (23%)	16 (62%)	<0.001
Nitrate	9 (6%)	7 (27%)	0.003
Statin	71 (49%)	16 (62%)	0.3
Left ventricular hypertrophy	1 (1%)	0	0.3
Q waves	32 (22%)	13 (50%)	0.007
ST-segment changes	4 (3%)	5 (19%)	0.003
Wall motion abnormalities at rest	51 (35%)	22 (85%)	<0.001
New wall motion abnormalities	15 (10%)	13 (50%)	<0.001
Abdominal aortic repair	58 (40%)	9 (35%)	0.7
Lower-extremity revascularisation	86 (60%)	17 (65%)	0.7

changes were also more common in patients with NT–pro-BNP levels ≥533 pg/ml.

DSE results: Heart rate increased from 73 ± 14 beats/min at rest to 133 ± 17 beats/min during peak stress. The maximum dose of dobutamine infusion was 36.8 ± 7 μg/kg/min. Atropine was administered in 52% of patients to achieve the target heart rate. Stress-induced myocardial ischemia occurred in 28 patients (16%). The mean number of ischemic segments in patients with stress-induced myocardial ischemia was 3.2 ± 1.2. No fatal complications occurred during or immediately after the stress tests.

NT–pro-BNP levels in relation to DSE results: The distribution of NT–pro-BNP was positively skewed, and the Mann-Whitney U-statistic test was used to compare NT–pro-BNP values in different groups. The median NT–pro-BNP level was higher in patients with wall motion abnormalities at rest during dobutamine stress echocardiography (397 pg/ml, interquartile range 178 to 710) compared with those without (59 pg/ml, interquartile range 34 to 118) (p <0.001). In the 39 patients with a history of congestive heart failure, the mean ejection fraction was 41 ± 15%. NT–pro-BNP levels were higher in patients with a history of congestive heart failure (median 338 pg/ml, interquartile range 85 to 846) compared with patients without a history of congestive heart failure (median 93 pg/ml, interquartile range 42 to 296) (p = 0.007). In the 39 patients with a history of congestive heart failure, the left ventricular ejection fraction was inversely correlated with the level of NT–pro-BNP (Pearson's R correlation = −0.59).

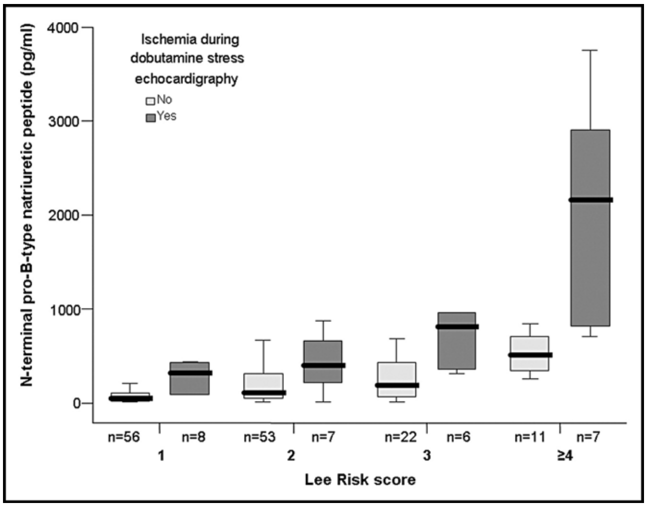

Figure 1. Correlation between median plasma NT–pro-BNP levels in patients with (p = 0.002) and without (p = 0.001) new wall motion abnormalities, divided into subgroups according to Lee et al's[3] risk score (high-risk type of surgery, coronary artery disease, history of congestive heart failure, history of cerebrovascular disease, diabetes mellitus, and renal dysfunction).[7] The box-and-whisker plot shows the median, upper and lower quartiles, and the range of the data.

A higher median NT–pro-BNP level was observed in patients with new wall motion abnormalities during dobutamine stress echocardiography (440 pg/ml, interquartile range 195 to 1,336) compared with those without (93 pg/ml, interquartile range 42 to 279) (p = 0.001). A direct relation was observed between the extent of stress-induced myocardial ischemia and NT–pro-BNP levels, with median levels of NT–pro-BNP of 364, 710, and 2,376 pg/ml in patients with 1 to 2, 3 to 4, and >4 ischemic segments, respectively (p for trend <0.001).

Figure 1 presents median NT–pro-BNP levels in patients with and without new wall motion abnormalites during dobutamine stress echocardiography, divided into subgroups according to cardiac risk score. In the group of patients with no new wall motion abnormalites during dobutamine stress echocardiography, the median NT–pro-BNP level increased from 51 pg/ml in patients with a risk score of 1 to 609 pg/ml in patients with a risk score of ≥4 (p for trend = 0.001). In the group of patients with new wall motion abnormalities during dobutamine stress echocardiography, the median NT–pro-BNP level increased from 321 pg/ml in patients with a risk score of 1 to 2,148 pg/ml in patients with a risk score of ≥4 (p for trend = 0.002).

Postoperative outcome: Postoperative cardiac events occurred in 13 patients (8%; cardiac death in 4 patients,

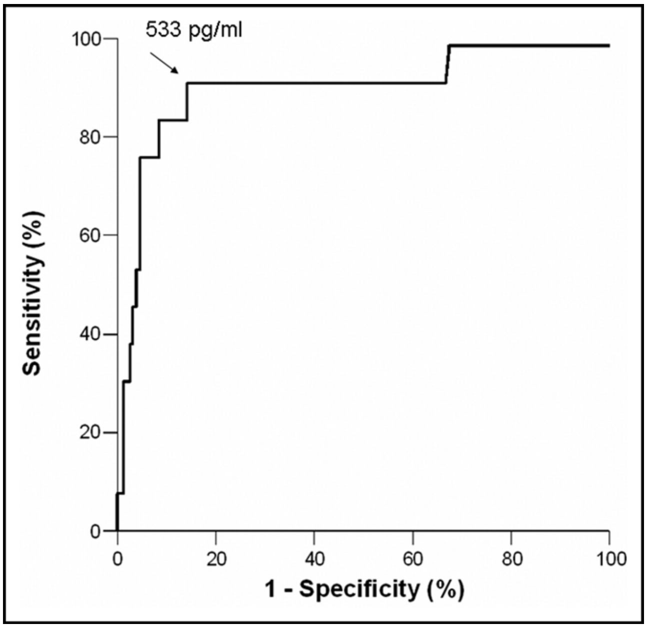

Figure 2. Receiver-operating characteristic curve of plasma NT–pro-BNP levels to predict postoperative cardiac events. Sensitivity and 1 − specificity are plotted for various NT–pro-BNP levels. The ideal cut-off value is indicated by the *arrow*.

nonfatal myocardial infarction in 9 patients). The median NT–pro-BNP level was higher in patients with cardiac events (939 pg/ml, interquartile range 634 to 2,469) compared with patients with no cardiac events (101 pg/ml, interquartile range 42 to 304) ($p < 0.0001$). Using receiver-operating characteristic curve analysis to predict postoperative cardiac events, a cut-off value of 533 pg/ml was identified as the optimal predictor of postoperative cardiac events (area under the curve 0.91; Figure 2). Using this cut-off value, NT–pro-BNP had a sensitivity of 85% and a specificity of 91%. Cardiac events were observed in 2 of 144 patients (1.4%) with NT–pro-BNP <533 pg/ml and in 11 of 26 patients (42%) with NT–pro-BNP ≥533 pg/ml ($p < 0.0001$). Of the 2 patients who experienced cardiac events despite low NT–pro-BNP levels (<533 pg/ml), 1 patient had a preoperative risk score of 1 and a new wall motion abnormality in 1 segment with no wall motion abnormalities at rest during dobutamine stress echocardiography, and the other patient had a preoperative risk score of 2 and only wall motion abnormalities at rest, with no new wall motion abnormalities during dobutamine stress echocardiography.

The postoperative cardiac event rate was 1 of 65 (2%) in patients with risk scores of 0 to 1 and 12 of 105 (11%) in patients with risk scores >1 ($p = 0.04$). Univariate predictors of cardiac events are listed in Table 2. Each 1-point increase in cardiac risk score was associated with an estimated risk of 3.6 (95% confidence interval 2.0 to 6.6, $p < 0.0001$) to develop postoperative cardiac events. In multivariate analysis, independent predictors of cardiac events were NT–pro-BNP level ≥533 pg/ml and new wall motion abnormalities during dobutamine stress echocardiography (Table 3).

Table 2
Univariate association of clinical characteristics, dobutamine stress echocardiographic results, and plasma NT–pro-BNP levels and the composite end point of cardiac death or nonfatal myocardial infarction

Variable	Odds Ratio	95% Confidence Interval	p Value
Age >70 yrs	1.1	0.3–4.3	0.9
Men	0.9	0.3–3.2	0.9
Angina pectoris	5.3	1.6–17.3	0.005
Previous myocardial infarction	3.7	1.1–12.5	0.04
Congestive heart failure	4.5	1.4–14.4	0.01
Previous cerebrovascular event	1.8	0.4–9.2	0.5
Previous coronary revascularisation	0.8	0.1–6.5	0.8
Hypertension	2.5	0.8–7.8	0.1
Diabetes mellitus	4.7	1.5–15.3	0.01
Hypercholesterolemia	0.6	0.2–2.0	0.4
Current smoking	0.8	0.2–3.6	0.7
Renal failure	34.2	5.5–212.4	<0.0001
Abnormal electrocardiography	2.5	0.8–7.9	0.1
Q waves	3.4	1.1–10.6	0.03
ST-segment changes	4.4	1.1–18.5	0.04
Wall motion abnormalities at rest	19.2	2.4–151.4	0.005
New wall motion abnormalities	25.6	6.4–101.6	<0.0001
Abdominal aortic repair	1.0	0.3–3.4	1.0
Lower-extremity revascularisation	1.1	0.4–3.4	0.9
NT–pro-BNP level per 100 pg/ml increase	1.20	1.1–1.3	<0.0001
NT–pro-BNP level ≥533 pg/ml	51.7	10.5–255.6	<0.0001

Table 3
Multivariate model to predict cardiac events in patients who undergoing major vascular surgery

Variable	Odds Ratio	95% Confidence Interval	p Value
NT–pro-BNP ≥533 pg/ml	17.2	2.8–106.4	0.002
New wall motion abnormalities	13.0	2.0–86.9	0.009
Diabetes mellitus	4.6	0.7–30.7	0.1
Renal failure	2.0	0.1–33.8	0.6
Wall motion abnormalities at rest	2.0	0.2–25.4	0.6

Discussion

Our study showed that elevated levels of NT–pro-BNP are significantly associated with an increased risk for postoperative cardiac events (cardiac death or nonfatal myocardial infarction) in patients who undergo major vascular surgery. The increased level of NT–pro-BNP was especially substantial for those with extensive stress-induced myocardial ischemia during dobutamine stress echocardiography. Using receiver-operating characteristic curve analysis, a NT–pro-BNP value of ≥533 pg/ml had the best prognostic value for postoperative cardiac events. This association between NT–pro-BNP and postoperative outcome was independent of clinical data, wall motion abnormalities at rest, and stress-induced myocardial ischemia.

In this study, NT–pro-BNP levels were measured, not

B-type natriuretic peptide levels. The half-life of NT–pro-BNP is considered to be 60 to 120 minutes, whereas the half-life of B-type natriuretic peptide is approximately 20 minutes.[6,7] Considering the longer half-life of NT–pro-BNP compared with B-type natriuretic peptide, NT–pro-BNP may be a superior screening marker in patients attending outpatient preoperative clinics.

Before surgery, patients are screened for coronary artery disease by vascular surgeons. Initial screening is performed using the revised cardiac risk index according to Lee et al.[3] High-risk patients are referred to cardiologists for additional stress testing to assess the presence and extent of coronary artery disease. As shown in this study, patients with greater risk scores have elevated NT–pro-BNP levels. It is important that those patients with stress-induced ischemia also have elevated NT–pro-BNP levels, and the increase in NT–pro-BNP level is related to the magnitude of stress-induced ischemia. Therefore, we speculate that NT–pro-BNP measurements can be used for initial screening in patients who undergo major vascular surgery. Those patients without risk factors and low levels of NT–pro-BNP represent a low-risk population, in which additional testing is not warranted. Patients with elevated NT–pro-BNP levels should be referred for additional stress testing to assess the presence and extent of coronary artery disease. Postoperative cardiac events may still occur in patients without stress-induced myocardial ischemia during preoperative dobutamine stress echocardiography. Elevated NT–pro-BNP levels may identify some patients at high risk despite the absence of inducible ischemia. The reason for the independent association of NT–pro-BNP levels with cardiac events after controlling for DSE results is not clear. Possible explanations include the greater sensitivity for detecting ischemia, the ability to reflect the occurrence of spontaneous ischemic episodes, and the objective nature of measurements compared with DSE interpretation.

In our study, the numbers of patients and events were small. However, our results are supported by a recently published study by Yeh et al,[8] who also found a significant association between NT–pro-BNP levels and cardiac complications in patients who underwent noncardiac surgery. Further studies are needed to confirm our findings in a larger population before recommending the use of NT–pro-BNP as a routine clinical investigation. Although the study has shown an additional value of NT–pro-BNP levels in defining risk, the management of these patients remains a challenge, because the Coronary Artery Revascularization Prophylaxis trial showed that coronary artery revascularization before elective vascular surgery does not significantly alter long-term outcomes.[9] However, several studies have demonstrated the beneficial effect of perioperative β-blocker therapy and minimal invasive surgery in reducing postoperative adverse events in high-risk patients who undergo major noncardiac surgery.[2,10,11] Patients with elevated NT–pro-BNP levels, with or without stress-induced myocardial ischemia, are at increased risk for adverse postoperative events and may therefore benefit from these management strategies.

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