**Predictive Value of Plasma N-terminal Pro B-type Natriuretic Peptide for Early Major Adverse Cardiac Event Following Elective Vascular Interventions**

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**Abstract**

**Objective:** Vascular interventions are associated with a substantial risk of major adverse cardiovascular events (MACEs) in perioperative period. We aimed to analyze the predictive value of plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) for early MACE following elective vascular intervention. **Materials and Methods:** We conducted a single-center, prospective, observational study at Jain Institute of Vascular Sciences, Bengaluru. One hundred and two patients undergoing elective vascular intervention were enrolled in the study. **Results:** A total of nine patients had MACE comprising seven acute coronary syndromes, one atrial fibrillation, and one congestive cardiac failure in perioperative period. Three patients had MACE preoperatively. Mean age was higher in MACE group (68 years vs. 62 years, \(P = 0.21\)). Receiver operator curve analysis demonstrated NT-ProBNP threshold cutoff \(>1580\) ng/ml and \(~>2020\) ng/ml pre- and post-operatively. In patients with MACE, mean plasma concentration of pre- and post-operative NT-proBNP was \(13,293.34\) ng/L and \(5628.84\) ng/L compared to non-MACE group of \(664.60\) ng/L and \(818.75\) ng/L, respectively. Positive and negative predictive values for pre- and post-operative NT-proBNP were \(24\%\), \(98.5\%\) and \(33\%\), \(98.8\%\), respectively. **Conclusion:** Presence of hypertension and elevated pre- and post-operative NT-proBNP values is significantly associated with higher incidence of early MACE (30 days) and is not influenced by age, gender, and previous coronary artery disease. NT-proBNP can be considered for the quantification of perioperative cardiac risk in vascular surgery patients.

**Keywords:** Cardiac event, elective vascular intervention, major adverse cardiovascular events, N-terminal pro B-type natriuretic peptide

**INTRODUCTION**

Vascular surgery includes operation on many of the high-risk patients in the present clinical practice.\(^1^\)\(^2\) Elective vascular interventions are associated with high cardiac morbidity and mortality in perioperative, immediate postoperative, and early (30 days) postoperative period.\(^3\) Myocardial injury as detected by a rise in troponin “I” concentration has been seen in only 38% of patients undergoing arterial revascularization for limb ischemia. Perioperative myocardial events are asymptomatic as analgesics masks chest pain and electrocardiography (ECG) shows non ST segment elevation myocardial infarction (NSTEMI) changes.\(^4\) Seventy percent of myocardial infarction (MI) in postoperative period is NSTEMI; hence, diagnosis is delayed in most of the cases. Over years, multiple scoring system and different modalities have been developed to assess perioperative cardiac risk of interventions but lack quantitative measures.\(^3\) Validated scoring systems are limited by their complexity and poor predictive values where cardiac interventions such as thallium stress testing and coronary angiography are limited by time and resources.\(^3\)

Rajagopalan et al.\(^5\) showed that in vascular patients, N-terminal pro B-type natriuretic peptide (NT-proBNP) has been an independent predictor of 30-day postoperative cardiac events as assessed by a composite end point of symptoms, troponin I levels, and ECG recordings. Systemic review and meta-analysis of seven studies by Karthikeyan

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et al.\textsuperscript{[6]} also supported NT-proBNP as an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery with an odds ratio of 19.3 (95% confidence interval [CI]: 8.5–43.7; $I^2 = 58\%$).

NT-proBNP is a 76 amino acid N-terminal inactive protein cleaved from proBNP to release brain natriuretic peptide. Blood levels of both BNP and NT-proBNP are used for screening, diagnosis of acute congestive heart failure, and both have been found useful to establish prognosis in heart failure as both markers are typically higher in patients with worse outcomes. A preoperative measure of NT-proBNP affords an easy and rapid opportunity to individually and objectively quantify perioperative cardiovascular risk.\textsuperscript{[7]}

Most of the studies had proved NT-proBNP as an independent predictor of major adverse cardiac events (MACEs). We aimed to analyze its predictive value in perioperative and early (30 days) postoperative period for our patient population at our tertiary care center.

**Materials and Methods**

Data were collected prospectively from 102 patients undergoing vascular intervention (open/endovascular/hybrid) from February 2015 to June 2015 at Jain Institute of Vascular Sciences, Bengaluru, India. Patients on active dialysis, venous interventions, urgent or emergency procedures, and patients without preoperative NT-proBNP values were excluded from the study. Patients undergoing thrombectomy were considered as emergency and excluded from the study. All the patients were evaluated preoperatively with arterial duplex, computed tomography/magnetic resonance angiography, and pulse volume recordings. The study protocol and informed consent were approved by the Institutional Review Board of the hospital, and all participants gave informed consent. Patient’s demographic data were recorded including age, gender, co morbidities, previous cardiac intervention, and history of chronic kidney disease (serum creatinine $>$ 1.5 mg/dl). Preoperatively, all patients underwent routine 12-lead ECG, two-dimensional echocardiography (2D-Echo), and were evaluated by cardiologist and anesthetist. Blood samples were obtained preoperatively and postoperatively at 24 h for the measurement of troponin I and NT-proBNP concentrations. An ECG was also obtained at the same time. Cardiologist who was blinded to the study data compared paired pre- and post-operative ECGs. 2D-Echo was done postoperatively when needed or suggested by cardiologist. Postoperatively, the patients were monitored in Intensive Care Unit or surgical ward when appropriate. The postoperative course was recorded. All patients were evaluated during their routine visits in outpatient department till 30 days postoperatively and were referred to cardiologist whenever needed.

Arrhythmias were defined as any change in baseline heart rhythm and excluded rate changes, as determined by ECG when clinically warranted. Myocardial injury was defined as a troponin elevation above laboratory’s upper limit of normal, and MI was defined following the new universal definition of MI – rise of cardiac biomarker (preferably troponin) above the 99\% percentile of the upper reference limit together with at least one other clinical factor such as symptoms of ischemia, ECG changes indicative of new ischemia (ST-T changes or new left bundle branch block), development of pathological Q-waves on the ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.\textsuperscript{[8]}

The end point of the study was development of any cardiac event comprising new arrhythmias, myocardial injury, MI, or need for cardiac catheterization in perioperative, immediate, and early (30 days) postoperative period following the elective vascular interventions.\textsuperscript{[3]}

Venous samples were collected from patients in pre- and post-operative period in ethylenediaminetetraacetic acid bulb. Values of NT-proBNP were obtained by AQT90 FLEX Analyzer (Radiometer Medical ApS; Denmark).

**Statistical analysis**

Chi-square ($\chi^2$) and Fisher’s exact tests were used for the analysis of categorical variables, and Student’s $t$-test was used for the analysis of continuous variables. Statistical significance was defined as $P < 0.05$. To identify the best discriminatory level of perioperative NT-proBNP associated with MACE, receiver operating characteristics (ROC) curves were analyzed and best cutoff defined as a value providing equal to the sensitivity and specificity. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

**Results**

Detailed demographic data of 102 patients are shown in Table 1. Ninety-nine patients underwent vascular interventions comprising 26 open, 69 endovascular, and 4 hybrid procedures which included bypass with/without angioplasty/stenting. On preoperative evaluation three patients were diagnosed to have coronary events and they all underwent coronary intervention by cardiologist and surgery was postponed in all of them.

Mean values of pre- and postoperative NT-proBNP were 664.60 ng/L (range, 600–23,000 ng/L) and 818.75 ng/L (range, 571–13,000 ng/L), respectively.

**Major adverse cardiac events**

Totally nine (six males, three females) patients had MACE comprising seven acute coronary syndrome, one atrial fibrillation, and one congestive cardiac failure. Mean age was higher in MACE group (67.56 years vs. 62.42 years, $P = 0.21$). The presence of hypertension was associated with higher incidence of MACE ($P = 0.0095$). One patient expired preoperatively and one in postoperative period. Age, gender, previous cardiac or renal dysfunction, and type of vascular intervention (open vs. endovascular) had no influence on perioperative cardiac events (POCEs).


Association of preoperative N-terminal pro B-type natriuretic peptide and cardiac events

Various studies had mentioned various cutoff limits for preoperative NT-proBNP to predict the risk of MACE. When ROC curve analysis done for our population, area under the curve (AUC) was 0.953 (95% CI: 0.893–0.985) [Figure 1]. The optimum discriminatory threshold derived was 1580 ng/L, yielding a sensitivity of 88.89% and a specificity of 93.55%. In MACE group, 8/9 patients had preoperative value above 1580 ng/L in comparison to 6/93 patients; which was statistically significant with $P < 0.0001$. PPV and NPV were 23% and 98.5%, respectively.

Table 1: Demographic data of patients

|                      | MACE (n=9) | No MACE (n=93) | P    |
|----------------------|------------|---------------|------|
| Male                 | 6          | 79            | 0.17 |
| Female               | 3          | 14            |      |
| Mean age (years)     | 67.56      | 62.42         | 0.21 |
| Diabetes mellitus    | 9          | 65            | 0.06 |
| Hypertension         | 9          | 50            | 0.009|
| Ischemic heart disease| 4         | 32            | 0.72 |
| Chronic kidney disease| 2        | 9             | 0.25 |
| Chronic obstructive pulmonary disease | 1 | 8 | 0.58 |
| Intervention         |            |               |      |
| Open surgery         | 1          | 25            | 0.72 |
| Endovascular surgery | 5          | 64            |      |
| Hybrid               | 0          | 4             |      |
| Preoperative NT-proBNP≤1580 | 1 | 87 | ≤0.00001|
| >1580                | 8          | 6             |      |
| Postoperative NT-proBNP≤2020 | 1 | 85 | ≤0.00001|
| >2020                | 5          | 8             |      |
| Mean preoperative NT-proBNP | 13,293.34 | 664.6 | ≤0.00001|
| Mean postoperative NT-proBNP | 5628.84 | 818.75 | ≤0.00001|

Three patients had cardiac event on preoperative evaluation. NT-proBNP: N-terminal pro B-type natriuretic peptide; MACE: Major adverse cardiac event

Association of postoperative N-terminal pro B-type natriuretic peptide and cardiac events

Association between postoperative NT-proBNP values and cardiac events is less reported in literature. ROC curve analysis in our study showed that AUC was 0.916 (95% CI: 0.843–0.962) [Figure 2]. The optimum discriminatory threshold derived was 2020 ng/L, yielding a sensitivity of 83.33% and a specificity of 91.40%. Five out of six patients had NT-proBNP levels above 2020 ng/L compared to 8 of 93 which was statistically significant with $P < 0.0001$. PPV and NPV were 33% and 98.8%, respectively.

DISCUSSION

There was no fixed cutoff limit for pre- and post-operative NT-proBNP to estimate the incidence of MACE in the available literature. Several studies reported that NT-proBNP is predictive of short- and long-term mortality and adverse cardiac events after noncardiac surgery and emergency surgery, but very few reported data are available concerning elective vascular interventions. Feringa et al. in a study of 335 surgical patients demonstrated NT-proBNP as better predictor of cardiac events than dobutamine stress Echo in surgical patients; the study included 117 vascular surgical patients. Schouten et al. evaluated 400 patients undergoing abdominal aortic aneurysm repair, including open surgery (70%) and endovascular repair (30%), peripheral bypass surgery, and carotid surgery and showed an additional prognostic value of NT-proBNP when combined with Revised Cardiac Risk Index (RCRI). The cutoff value in this study was 350 pg/ml (pg/ml = ng/L). However, despite a numerical increase in the AUC of NT-proBNP in addition to RCRI, statistical significance was not achieved in their study.

Yang et al. showed that preoperative measurement of NT-proBNP provides information useful for the prediction of POCE as a single parameter in high-risk patients undergoing noncardiac vascular surgery and cutoff value in their study...
was >302 pg/ml. A recent meta-analysis of NT-proBNP for the prediction of POCE summarized that the decision threshold used in the previous studies varied between 201 and 533 pg/ml for NT-proBNP. In our study, optimal cutoff for pre- and post-operative NT-proBNP is 1580 ng/ml and 2020 ng/ml, respectively. In our study, cutoff values of NT-proBNP were higher than other reported studies, which might be because of different geographical population. Postoperative values of NT-proBNP were also predictive of postoperative cardiac events although troponin levels were normal, this is the difference that we found compared to older studies.

This study is of single-center experience with small number of candidates, and more variables such as duration of surgery, blood transfusion, and other factors contributing to perioperative cardiac stress may have been included with large population which is required to assess the significance of NT-proBNP in perioperative period.

**Conclusion**

Our results suggest that perioperative NT-proBNP measurement can help to identify patients at high risk for MACE before and after elective vascular interventions. These patients should be considered for optimal cardiac evaluation before proceeding for elective vascular interventions and considered for targeted postoperative cardiac interventions to improve short-term outcome. Larger studies are needed to suggest a threshold value in the perioperative setting and to examine the potential impact of early intervention.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Berry C, Kingsmore D, Gibson S, Hole D, Morton JJ, Byrne D, et al. Predictive value of plasma brain natriuretic peptide for cardiac outcome after vascular surgery. Heart 2006;92:401-2.

2. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery – Executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation 2002;105:1257-67.

3. Causey MW, McVay DP, Oguntoye M, Andersen C, Singh N. Application of preoperative brain natriuretic peptide levels in clinical practice. Vascular 2013;21:225-31.

4. Badner NH, Knill RL, Brown JE, Novick TV, Gelb AW. Myocardial infarction after noncardiac surgery. Anesthesiology 1998;88:572-8.

5. Rajagopalan S, Croal BL, Bachoo P, Hillis GS, Cuthbertson BH, Brittenden J. N-terminal pro-B-type natriuretic peptide is an independent predictor of postoperative myocardial injury in patients undergoing major vascular surgery. J Vase Surg 2008;48:912-7.

6. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, et al. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiac outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. J Am Coll Cardiol 2009;54:1599-606.

7. Wayne Causey M, Singh N. Clinical implications of B-type natriuretic peptide and N-terminal pro – B-type natriuretic peptide in the care of the vascular surgery patient. Semin Vasc Surg 2014;27:143-7.

8. Archan S, Fleisher LA. From creatine kinase-MB to troponin: The adoption of a new standard. Anesthesiology 2010;112:1005-12.

9. Feringa HH, Bax JJ, Ellhendy A, de Jonge R, Lindemans J, Schouten, et al. 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. The American Journal of Cardiology 2016;98:111-5.

10. Schouten O, Hoeks SE, Goei D, Bax JJ, Verhagen HJ, Poldermans D. Plasma N-terminal pro-B-type natriuretic peptide as a predictor of perioperative and long-term outcome after vascular surgery. J Vasc Surg 2009;49:435-41.

11. Yang JH, Choi JH, Ki YW, Kim DI, Kim DK, Park JR, et al. Plasma N-terminal pro-B-type natriuretic peptide is predictive of perioperative cardiac events in patients undergoing vascular surgery. Korean J Intern Med 2012;27:301-10.