

N-terminal pro B type natriuretic peptide in high cardiovascular-risk patients for noncardiac surgery: What is the current prognostic evidence?

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ABSTRACT

As millions of surgical procedures are performed worldwide on an aging population with multiple comorbidities, accurate and simple perioperative risk stratification is critical. The cardiac biomarker, brain natriuretic peptide (BNP), has generated considerable interest as it is easy to obtain and appears to have powerful predictive and prognostic capabilities. BNP is currently being used to guide medical therapy for heart failure and has been added to several algorithms for perioperative risk stratification. This review examines the current evidence for the use of BNP in the perioperative period in patients who are at high-cardiovascular risk for noncardiac surgery. In addition, we examined the use of BNP in patients with pulmonary embolism and left ventricular assist devices. The available data strongly suggest that the addition of BNP to perioperative risk calculators is beneficial; however, whether this determination of risk will impact outcomes, remains to be seen.

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INTRODUCTION

Millions of surgical procedures are performed worldwide, many in high-risk cardiovascular patients, and a significant portion of these patients sustain myocardial injury postoperatively. To get a better perspective what exactly this means, in the POISE trial (whose primary intention was to evaluate the use of beta blockers), over 8300 patients were evaluated and in those at risk for cardiovascular disease, 6.9% had perioperative major adverse cardiovascular events (MACEs) within 30 days of surgery.^[1] Cardiac complications, including death, myocardial infarction (MI), and congestive heart failure (CHF) are the leading causes of death in these patients. The ability to accurately identify and risk stratify such patients would allow both clinicians and patients to make informed decisions about surgical procedures and medical therapy, both intra- and post-operatively. Some examples include alterations in the choice of anesthetic technique and of whether

postoperative monitoring or intensive care is necessary. The need for a simple, precise, and cost-effective screening test to identify such patients at risk is paramount. Current risk stratification guidelines for perioperative evaluation are evolving, but the revised cardiac risk index (RCRI) has been widely used.^[2] These guidelines, which are endorsed by several major international societies, are the current standard of care;^[3] however, their predictive ability has been called into

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question^[4] and thus the need for improved preoperative evaluation and risk stratification exists.

The presence of cardiac biomarkers and their predictive ability, whether preoperative or postoperative, has generated considerable interest as an additional screening tool, and may actually be better at predicting major adverse cardiac events than other standard methods.^[5] Advantages include ease of obtaining results, dynamic nature correlating with the state of the disease, and objectivity, which is especially important in the postoperative period when many patients may be asymptomatic. Use of biomarkers in cardiac risk has been considered, so important is that the American Heart Association released a scientific statement on criteria for evaluation of novel markers before they are used in clinical practice.^[6]

BRAIN NATRIURETIC PEPTIDE PHARMACOLOGY

Brain natriuretic peptide (BNP) is a hormone involved in sodium and water homeostasis as well as myocardial function. It is primarily released by the ventricles of the heart during conditions of ischemia, myocardial stretch, and other stimuli. Elevated levels are diagnostic of heart failure and predictive of cardiac death,^[7] especially in those with severe CHF as defined by the left ventricular (LV) ejection fraction of <25%.^[8] In addition, in specific situations such as acute coronary syndrome and stable angina, increasing levels of BNP have been associated with increased mortality.^[9,10]

The prohormone proBNP is cleaved into a biologically active fragment (BNP) and an N-terminal fragment that is inert (NT-proBNP). BNP is involved with heart failure and has diuretic, natriuretic, and vasodilator effects. It has also been shown to inhibit the renin-angiotensin system, endothelin secretion, and systemic and renal sympathetic activity.^[11] Many assays are available for the measurement of plasma BNP with varying clinical ranges. In healthy patients, levels of BNP and NT-proBNP are similar, but in patients with heart failure, NT-proBNP rises significantly. Older patients and women have higher levels of BNP, so age and gender should be taken into account as well as the degree of renal dysfunction. Renal failure is associated with elevated BNP and even greater elevations in NT-proBNP as there is dependence on adequate renal function for clearance. This translates into the lower specificity of NT-proBNP for adverse cardiac events.^[12] Further confusion arises in that NT-proBNP levels have a longer half-life than BNP and are present in much higher

concentrations in the serum. Which level to monitor, i.e. BNP or NT-proBNP, remains unclear. Although both have good clinical performance, NT-proBNP has a wider range and is less subjected to rapid change in levels due to its longer half-life, which is one to 2 h. Some studies have found NT-proBNP to be superior in the prediction of morbidity and mortality, likely attributable to above factors.^[13]

NATRIURETIC PEPTIDES IN HEART FAILURE

Although it still remains somewhat controversial, natriuretic peptides have recently been used to guide therapy for heart failure as levels are stable in patients who have stable disease, but they rise with decompensation or ischemia.^[14,15] Inadequate therapy for heart failure, with dosing of angiotensin-converting enzyme inhibitors, beta blockers, and diuretics that are too low may be to blame for elevated levels of BNP as appropriate, and aggressive medical therapy for heart failure causes a fall in peptide levels.^[16] In the TIME-CHF trial, the authors sought to discern whether BNP-guided therapy for heart failure was superior to standard medical therapy in older patients (>75 years of age).^[17] Patients older than 60 years with New York Heart Association Class II symptoms, a BNP level >400 pg/mL comprised one group and patients older than 75 with a BNP >800 pg/mL comprised the elderly group. Their results demonstrated a positive effect in the younger patient group receiving BNP-guided therapy including reduced mortality and heart failure-related adverse events; however, this advantage was not seen in older patients. In the PROTECT trial, 151 patients were enrolled, and BNP-guided therapy was compared with standard medical therapy. Patients whose therapy was guided by BNP levels demonstrated improvements in the quality of life, improved LV ejection fraction, and reduced event rates.^[18,19] A meta-analysis of randomized controlled trials performed by Porapakkham *et al.* examined BNP-guided heart failure therapy. They concluded that using BNP to guide heart failure therapy decreases all-cause mortality, especially in patients who were younger than 75 years of age.^[20] This is especially important as heart failure is actually associated with higher perioperative mortality than coronary artery disease^[21] as well as being a leading cause of hospitalization and re-hospitalization.^[22] In addition to use in outpatient heart failure therapy, plasma BNP levels are also used for prognosis and perioperative risk stratification. This review will focus on whether measurement of plasma BNPs can provide prognostic information and/or risk stratification for

patients at high-cardiovascular risk when undergoing noncardiac surgery.

BRAIN NATRIURETIC PEPTIDE AND PERIOPERATIVE RISK

Current perioperative risk stratification relies on clinical risk factors and scoring systems. In one of the first large studies to assess the value of BNP in perioperative risk, 1590 patients were evaluated before noncardiac surgery.^[23] They were risk stratified based on both the Goldman criteria^[24] and BNP, with levels above 300 pg/mL are considered to be high-risk and ≥ 189 pg/mL was the cutoff point for elevation. Overall, adverse cardiac events occurred in 6% of patients. In those who were at high risk based on the BNP level, 81% had a MACE versus 14% of those who were at high risk by Goldman criteria. They also noted that over seventy patients could have been saved a cardiac event if BNP had been used instead of Goldman criteria in one group. A significant percentage of patients who were in Goldman Class I or II had events that were not predicted by this classification, but were based on BNP. Overall, BNP was deemed to be superior at perioperative risk assessment when compared to the Goldman criteria. It was also concluded that BNP was an independent predictor for preoperative cardiac risk.

A 2009 meta-analysis that assessed whether NT-proBNP was an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery included 7 studies of 2841 patients who had a preoperative BNP measurement. They found that there was a statistically significant association between a preoperative elevation in serum BNP and the adverse cardiovascular outcomes of death, cardiac death, and nonfatal MI at 30 days.^[25] Indeed, preoperative BNP was a strong predictor for MACE independent of clinical risk factors. Another meta-analysis involving over 4800 patients examining long-term mortality using BNP and NT-proBNP levels and their role in the prediction of mortality and MACE in noncardiac surgery was conducted by Ryding *et al.* They focused on preoperative measurement and assessed both short- (~1 month) and long-term (>6 months) mortality. They found MACE to occur in 32.8% of patients with elevated BNP as compared to 4% of patients who did not have elevations in preoperative BNP, and this was consistent for both BNP and NT-proBNP.^[26] In terms of all-cause mortality, this occurred in 11.7% of patients with elevated BNPs as opposed to 0.81% whose BNPs were in the normal range. Elevated short-term risk of cardiac death was seen here as well. They concluded that elevated BNPs increased the risk of both short- and

long-term MACE, cardiac mortality, and all-cause mortality. These findings were confirmed by yet another meta-analysis conducted in 2011 by Rodseth *et al.* that evaluated mortality at 6 months or later postoperatively and came to a similar conclusion.^[5] They looked exclusively at the ability of preoperative BNP levels to predict all-cause mortality. They found the positive predictive value to be 0.24 and the negative predictive value to be 0.94. Essentially, they confirmed that elevated preoperative BNP levels were associated with all-cause mortality >6 months postoperatively, but the negative predictive value was much greater than positive predictive value. In addition, BNP concentrations below cutoff points in individual studies were highly predictive of survival.

The value of postoperative BNP measurement is a bit less clear, but has been addressed. The relationship between postoperative BNP and cardiovascular outcomes was evaluated in a 2013 meta-analysis of 18 studies and over 2000 patients in which BNP was obtained within a week of noncardiac surgery. The primary outcome of death (cardiac or not), coronary revascularization, heart failure, or nonfatal MI at 30 days occurred more often in patients with a BNP ≥ 245 pg/mL or an NT-proBNP ≥ 718 pg/mL.^[27] The risk elevation was sustained to 180 days postoperatively. They also evaluated risk using BNP as a continuous variable, with higher values being associated with a higher event rate. Whether postoperative analysis provides additional necessary information to preoperative risk stratification and evaluation or whether it will change the outcome remains to be seen. The authors addressed this question in a later study as they assessed whether the addition of postoperative BNP levels enhanced the ability to predict death or nonfatal MI at 30 and 180 days.^[28] There were 2179 patients in this analysis with vascular surgery appearing as the most common procedure. The same thresholds of BNP and NT-proBNP were used. Interestingly, 76% of patients in the study had increases in BNP postoperatively and 23% had a decrease from preoperative levels. They found that addition of the postoperative BNP level improved the predictive capacity for death or nonfatal MI at both time points, potentially allowing intervention before event occurrence. Again, however, it is not clear whether this will improve patient outcomes. A final meta-analysis that focused on a mixed surgical population of 5438 patients reached similar conclusions – that elevated perioperative BNP levels were associated with postoperative MACE,

but that postoperative levels had better predictive ability than preoperative.^[29] However, this study did include some cardiac surgical patients, which were not addressed by any of the other studies.

Whether this enhanced predictive ability will translate into improved outcomes is yet to be determined. What it will allow for is preemptive intervention such as medical therapy, coronary revascularization, or higher levels of monitoring in selected patients which could certainly be beneficial and reduce the number of MACEs in the perioperative period.

BRAIN NATRIURETIC PEPTIDE IN VASCULAR SURGICAL PATIENTS

As we have learned, predicting MACE after noncardiac surgery is not a straightforward task, and this is especially true in vascular surgical patients, who often have major and multiple comorbidities, where conventional risk calculators appear to fall short.^[30] Many diagnostic tests such as electrocardiogram, nuclear myocardial studies, dipyridamole echo, and dobutamine stress echo have been studied with dobutamine stress echocardiography (DSE) showing the best correlation with perioperative ischemia detection.^[30] However, studies have suggested that preoperative BNP levels may be a better prognostic test than DSE, particularly in vascular surgical patients.^[31-33] Vascular surgical patients are at higher risk, as by definition, they have more extensive disease burden and higher rates of perioperative morbidity and mortality.^[34] A 2008 meta-analysis by Rodseth *et al* of the ability of preoperative BNP and NT-proBNP to predict postoperative mortality/MACE found that BNP and NT-proBNP were at least as predictive of MACE as DSE.^[35] Others have found that postoperative, rather than preoperative, levels of NT-proBNP were a better predictor of MACE in vascular surgery patients.^[36]

An individual patient data meta-analysis examined whether BNP risk stratification alone would be improved with the addition of clinical risk factors and compared BNP alone, BNP plus RCRI, and RCRI alone in 850 vascular surgical patients. Patients were initially stratified according to BNP level as low, intermediate, or high risk. They then added clinical risk factors and ultimately found that RCRI risk factors did not improve the overall risk stratification when compared with BNP alone for MACE, and none of the RCRI factors were independent predictors of adverse events.^[33] This lends yet further strength to recommendations that BNP levels

have to be incorporated into preoperative evaluation algorithms. Postoperative troponins have also been evaluated in similar fashion in vascular surgical patients and it was found that there was an increase in mortality and morbidity with elevated levels.^[37] Furthermore, the degree of troponin elevation directly correlated with mortality. Postoperative troponin measurement is already recommended in high-risk patients;^[38] however, they do not have the preoperative value in risk stratification that BNP appears to have.

It should be noted that a significant problem and weakness with many of the above meta-analyses discussed is the lack of a universal cut-off point or discriminatory threshold for BNP and lack of standardized assay methods for obtaining the levels. In fact, the use of study-specific thresholds in meta-analyses was found to overestimate the prognostic utility of NT-proBNP.^[39] This phenomenon can be applied to other meta-analyses that use this particular methodology. Rodseth *et al*.^[35] determined that the large variability in discriminatory thresholds did not allow them to draw firm conclusions regarding the prognostic utility of BNP/NT-proBNP in vascular surgical patients in earlier studies. The authors suggest that biomarkers should be evaluated as a continuous variable instead.

BRAIN NATRIURETIC PEPTIDE IN PULMONARY HYPERTENSION AND PULMONARY EMBOLISM

As BNP is elevated in conditions of myocardial stretch, it is not only LV enlargement or ischemia that will cause release, but also right ventricular (RV) strain. Such examples include pulmonary embolism (PE), pulmonary hypertension, and biventricular failure. In hemodynamically significant acute PE, RV strain can be detected on echocardiography and is associated with higher mortality and morbidity.^[40,41] BNP has been found to be elevated in over 80% of patients with hemodynamically significant PE.^[42] Levels were higher in patients with massive PE versus lesser grades of PE as well.

BNP levels were found to have prognostic value in this situation as well. A study by Kucher *et al*. looked at patients who were symptomatic.^[43] Adverse events occurred in 20/73 patients and these patients had significantly elevated BNP. Patients with low BNP had a benign clinical course, giving the test a high-negative predictive value. Looking at hospital mortality prediction, BNP and hypoxemia by pulse oximetry were significant, even though current guidelines dictate that

risk assessment in acute PE is determined on clinical and echocardiographic parameters.^[44] Chronic RV dysfunction accompanying pulmonary hypertension is also associated with elevated levels of BNP and that elevated levels were associated with decreased survival.^[45]

BRAIN NATRIURETIC PEPTIDE IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES

Implantation of left ventricular assist devices (LVADs) is becoming more common as technology improves and indications for implantation expand. Currently, LVAD may be used not only as a bridge to transplantation, but also as destination therapy. In general, BNP levels appear to decrease after device implantation.^[46-48] Elevated levels immediately or shortly after implantation signify problems such as device malfunction, persistent RV failure, and nonoptimal LVAD settings.^[48] Levels also changed with changes in pump speed, often with decreases in response to increases in revolutions per minute. In addition to short-term management, BNP appears to have longer-term prognostic value in LVAD patients as well. In a study of 83 LVAD patients, Sato *et al.* demonstrated that patients' BNP levels measured at 60 days after implantation were able to predict all-cause mortality and that those with high BNP (cut-off value was 322 pg/mL) had significantly decreased survival at 2 years.^[49] Using BNP to guide immediate postoperative management also resulted in a significantly reduced length of stay in the hospital, although there was no change in mortality or readmission rate.^[47] BNP in these circumstances helped to guide inotrope and diuretic use as well as device speed changes. BNP may also help predict which patients will eventually be weaned from the LVAD. In a small, retrospective study looking at patients who were able to be weaned versus those who were not, BNP levels were significantly lower at 1 and 3 months in the patients who had a recovery of native heart function.^[50] Overall, this is an area of emerging interest, and more study is needed to determine the role of BNP in LVAD patients.

CONCLUSION

Given the millions of patients who will experience MACEs in the perioperative period, perioperative identification of patients at risk has several advantages. Among such advantages include modification of surgical procedures, deferral of surgery, potential intervention preoperatively, and the ability to tailor therapy

postoperatively. It is fairly clear that the existing data strongly suggest that incorporation of measurement of preoperative plasma BNP would be beneficial. In fact, it is compelling enough that the European Society of Cardiology and the European Society of Anesthesiology guidelines for preoperative risk assessment recommend obtaining preoperative BNP levels.^[51]

Measurement of even one BNP level, when elevated, can enhance preoperative risk stratification and more patients can be correctly classified as low or high risk. As optimal cut-off values are still controversial, further study is necessary in this arena to define a precise screening value. At a minimum, an elevated preoperative BNP should necessitate further testing such as stress echocardiography or cardiac catheterization. Of the studies included in this review, a level of >189 pg/mL may be considered elevated, and may fall into the category of requiring further investigation. Adding biomarker levels to preoperative and postoperative evaluation may serve to improve outcomes as they may identify patients who have clinically silent disease – these patients can then be placed on appropriate medical therapy. Large, well-designed, and powered prospective studies are needed to address this question.

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Conflicts of interest

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