Preoperative Natriuretic Peptides in Noncardiac Surgery: When and How to Use for Cardiac Risk Evaluation

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ABSTRACT

Cardiac risk evaluation is a central component of most preoperative evaluation of adults undergoing noncardiac surgery. Many tools are available for preoperative cardiac assessment including cardiac risk scores, electrocardiogram, cardiac imaging, and cardiac stress tests. Biomarkers, and more specifically natriuretic peptides, have also been found to provide additional value for preoperative cardiac risk stratification and their routine use in at-risk patients have been recommended in recent perioperative guidelines.

RÉSUMÉ

L'évaluation des risques cardiaques est un élément central de la plupart des évaluations préopératoires des adultes subissant une chirurgie non cardiaque. De nombreux outils sont disponibles pour l'évaluation cardiaque préopératoire, notamment les scores de risque cardiaque, l'électrocardiogramme, l'imagerie cardiaque et les tests d'effort cardiaque. On a également constaté que les biomarqueurs, et plus particulièrement les peptides natriurétiques, apportent une valeur supplémentaire pour la stratification du risque cardiaque préopératoire et leur utilisation systématique chez les patients à risque a été recommandée dans de récentes lignes directrices périopératoires.

Introduction

Cardiac risk evaluation is a central component of most preoperative evaluation of adults undergoing noncardiac surgery. Many tools are available for preoperative cardiac assessment including cardiac risk scores, electrocardiogram, cardiac imaging, and cardiac stress tests. Biomarkers, and more specifically natriuretic peptides, have also been found to provide additional value for preoperative cardiac risk stratification and their routine use in at-risk patients have been recommended in recent perioperative guidelines.^{1,2}

In this review, we will provide an overview of the physiological and analytic considerations regarding natriuretic peptides, discuss their utility for preoperative cardiac risk stratification in addition to clinical evaluation, and discuss indications for preoperative natriuretic peptides testing. We will also address the potential benefit of natriuretic peptides testing in patients with cardiovascular disease and discuss conditions associated with elevated natriuretic peptides that are relevant to the perioperative setting.

The Heart: An Endocrine Organ

Almost 40 years ago, it was first reported that atrial myocardium extracts contained biologically active peptides that when injected to non-diuretic rats, induced a rapid and potent natriuresis and diuresis, along with potassium excretion.³ Following this original observation, this field of research evolved to revise the role of the heart as no longer a mere valve-and-muscle pump, but a complex organ that exerts an endocrine function, playing a key role in cardiovascular and renal regulation.⁴ Cardiac natriuretic hormones include atrial natriuretic peptide and brain natriuretic peptide (BNP) and are predominantly produced by cardiomyocytes. BNP mainly originates from ventricles and is released as a prohormone, proBNP, which is subsequently split into the inactive N-terminal peptide (NT-proBNP), and the active hormone, BNP.⁵ Both peptides are released in equimolar proportions and represent the same hormonal activity. However, because of different clearance mechanisms, of which 15–20% is by the kidneys, BNP has a half-life of 20 min and NT-proBNP of 120 min and NT-proBNP serum concentrations are approximatively six times higher than BNP.^{5–7}

Electron microscopy of ventricular cardiomyocytes show that under physiological conditions (i.e., a healthy heart), secretory granules of proBNP are found only in limited amounts.⁴ On the other hand, markedly high levels of natriuretic peptides found in patients with chronic heart failure suggest a resistance to the biological effects of BNP, which at such high levels is no longer biologically active.^{4,8}

Several pathophysiological mechanisms increase production and release of BNP, including mechanical, inflammatory, ischemic, hemodynamic, and other humoral stimuli.⁴ Ventricular stretch and mechanical strain were initially considered the main mechanisms for increased BNP production and release.⁹ Angiotensin-II,⁵ arginine vasopressin,¹⁰ and α -adrenergic agents¹¹ are some of the peptides involved in hemodynamic response that have been found to stimulate BNP production/release. Proinflammatory and inflammatory response factors such as endothelin-1,¹² cytokines (i.e., interleukin-1, interleukin-6, tumor necrosis factor- α),¹³ and prostaglandins¹⁴ all up-regulate the expression of BNP. Thyroid hormones,¹⁵ corticosteroids,¹⁵ and estrogens¹⁶ also increase BNP; conversely, androgens inhibit BNP production, likely explaining small sex variation that can be observed in BNP/NT-proBNP levels.¹⁷ Another important mechanisms leading to BNP/NT-proBNP release is myocardial hypoxia, ischemia, and fibrosis.^{5,18}

Natriuretic Peptides as an Alternative to Cardiac Imaging for Preoperative Cardiac Risk Stratification

Biomarker use for cardiac risk stratification in the perioperative setting has gained interest in the recent decades and BNP/

NT-proBNP have the most compelling evidence for their use in clinical practice.¹ They offer an alternative to cardiac imaging (e.g., echocardiogram, cardiac stress testing) that is less expensive and does not require patients to come back to the hospital, potentially avoiding surgical delays.

Park et al.¹⁹ compared the predictive performance of a preoperative echocardiogram and NT-proBNP in addition to clinical evaluation using the Revised Cardiac Risk Index (RCRI)²⁰—a commonly used clinical risk score—to predict postoperative major cardiac events (PMCE) after noncardiac surgery. The authors found that compared to an RCRI score ≥ 2 (relative risk [RR] 1.35, 95% confidence interval [CI] 1.02–1.76), adding echocardiography findings of left ventricular ejection fraction (LVEF) $< 50\%$ resulted in only minimal change in risk prediction (RCRI + LVEF: RR 1.82, 95% CI 1.39–2.35). In contrast, the addition of an elevated preoperative NT-proBNP ≥ 301 ng/L to RCRI was associated with a significantly higher risk of PMEC (RCRI + NT-proBNP: RR 3.72, 95% CI 2.73–4.96). A reduced LVEF added to both RCRI and NT-proBNP did not result in a meaningful change in risk prediction (RCRI + NT-proBNP + LVEF: RR 3.96, 95% CI 2.88–5.33). Many studies have looked at the prognostic value of preoperative cardiac stress testing (i.e., stress echocardiogram and nuclear stress testing) but none have looked at the risk prediction improvement beyond the use of clinical risk scores or compared to BNP/NT-proBNP.²¹ Another study looking at the prediction value of coronary computed tomographic angiography (CCTA) in addition to RCRI found that CCTA improved risk discrimination only for patients who had a postoperative cardiac event. For patients who did not have a postoperative cardiac event, CCTA inappropriately overestimated patients' perioperative cardiac risk.²² The study did not compare CCTA to BNP/NT-proBNP. Studies on preoperative coronary revascularization prior to noncardiac surgery have shown conflicting results on preventing perioperative cardiac events.^{23,24}

One hypothesis behind the limited utility of preoperative cardiac imaging for risk stratification is that coronary anatomy may not be the most dominant factor driving perioperative cardiac risk. In other words, an image may not be as informative on the heart's health and physiology as a biological marker. This may explain why studies of routine preoperative BNP/NT-proBNP in patients with baseline risk factors have shown more compelling evidence for preoperative cardiac risk prediction than studies on cardiac imaging.

Preoperative Natriuretic Peptides in Noncardiac Surgery

A great number of studies summarized in several systematic reviews have consistently demonstrated the association between preoperative BNP/NT-proBNP levels and postoperative

cardiovascular outcomes after various types of noncardiac surgery.^{25–27} An individual patient-data systematic review that included 18 cohorts ($n = 2179$) found that a preoperative BNP threshold of 92 ng/L and NT-proBNP of 300 ng/L had the strongest association with postoperative death and nonfatal myocardial infarction at 30 days.²⁸ This review also demonstrated that the addition of the BNP/NT-proBNP thresholds significantly improved preoperative risk discrimination in one-third of patients (Net Reclassification Improvement 31.6%).

More recently, the VISION NT-proBNP study assessed the association between preoperative NT-proBNP and postoperative cardiac events in an international, prospective cohort of 10,402 patients.²⁹ Patients who were 45 years or older undergoing noncardiac surgery with at least an overnight hospital stay had NT-proBNP measured preoperatively and were followed for 30 days.²⁹ Preoperative NT-proBNP thresholds of <100 ng/L, 100 to <200 ng/L, 200 to <1500 ng/L, and ≥ 1500 ng/L were associated with a 30-day incidence of the composite of all-cause mortality or myocardial infarction of 1.7, 3.0, 7.9, and 15.8%, respectively.²⁹ The addition of preoperative NT-proBNP thresholds to RCRI score improved classification of cardiac risk of one in four patients (Net Absolute Reclassification Improvement 25.8%). Based on the Canadian Cardiovascular Society (CCS) recommendation for testing in patients with baseline risk $\geq 5\%$ and the results from this study, a preoperative NT-proBNP threshold of ≥ 200 ng/L (instead of ≥ 300 ng/L) may provide better discrimination of perioperative cardiac risk. An online calculator is available that can provide perioperative cardiac risk estimates based on RCRI risk factors and NT-proBNP from the VISION NT-proBNP study (https://qxmd.com/calculate/calculator_783/vision-perioperative-risk-using-nt-probnp). Another recent prospective cohort ($n = 1401$) that assessed preoperative functional capacity and preoperative NT-proBNP in noncardiac surgery also found that the addition of preoperative NT-proBNP to RCRI improved classification of risk in 25% of patients to predict 30-day myocardial infarction or mortality; no specific thresholds were reported.³⁰

Recommendations for Preoperative Cardiac Testing in the Clinical Setting

Most perioperative guidelines have de-escalated the importance of cardiac imaging for routine preoperative cardiac risk stratification, and some now recommend natriuretic peptides testing. Choosing wisely Canada recommends against routine preoperative echocardiogram and cardiac testing in asymptomatic patients undergoing low to intermediate-risk noncardiac surgery.³¹ The CCS Perioperative Guidelines recommend against routine preoperative echocardiogram and cardiac stress test.¹ According to the CCS perioperative guidelines, cardiac testing should be targeted to patients who present signs or symptoms

suggestive of undiagnosed unstable or severe cardiac disease (e.g., Class III–IV or unstable angina, cardiomyopathy, severe aortic stenosis, pulmonary hypertension).¹ The European and American guidelines still recommend routine cardiac imaging but more recent iterations of their guidelines restrict it to higher risk patients.^{2,32}

The CCS perioperative guidelines recommend BNP/NT-proBNP testing in patients with baseline risk of postoperative cardiac events $\geq 5\%$, that is, age ≥ 65 years, RCRI score ≥ 1 , or age 45–64 with significant cardiovascular disease (Strong recommendation; Moderate-Quality Evidence).¹ In patients with preoperative BNP ≥ 92 ng/L or NT-proBNP ≥ 300 ng/L, the guidelines recommend postoperative surveillance for cardiac events, including daily troponin for the first 48–72 h after surgery. The 2014 European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA) perioperative guidelines also recommend BNP/NT-proBNP measurements in high-risk patients (i.e., functional capacity ≤ 4 METs, RCRI score ≥ 2 in patients undergoing vascular surgery, and RCRI score ≥ 3 for non-vascular surgery) (Level IIb recommendation).² The American College of Cardiology (ACC) and American Heart Association preoperative guidelines do not currently recommend preoperative BNP/NT-proBNP testing, but other national guidelines and anesthesia society's do.^{33,34}

BNP and NT-proBNP are both commercially available assays for use in clinical settings, although most centers will have access to either one but not both. Point-of-care tests are also available for both biomarkers.³⁵ The laboratory range and upper reference limit (URL) between assays and manufacturers differ and there is no true correction factor that allows one to convert values between BNP and NT-proBNP. Both assays can be reported either in pmol/L (SI units) or ng/L (conventional units) and attention should be paid to the unit when using specific cut-offs reported in the literature. Conversion between pmol/L to ng/L can be done by multiplying by 3.5 for BNP and 8.5 for NT-proBNP levels.³⁶

Management of Patients with Elevated Natriuretic Peptides

Preoperative BNP/NT-proBNP can be used for informed-consent and shared-decision making regarding surgery and, if elevated, postoperative troponin monitoring for the first 48–72 h is recommended.¹ In the authors' experience, preoperative BNP/NT-proBNP can also be useful to guide preoperative management. Most perioperative guidelines recommend performing cardiac testing in patients with signs or symptoms suggestive of ischemic heart disease or cardiomyopathy, such as new or worsen angina or exertional dyspnea.^{1,2,32} During preoperative evaluation, it can be challenging to determine if dyspnea on exertion is related to

ischemic heart disease or other noncardiac conditions such as deconditioning (e.g., patient awaiting hip replacement surgery with loss of functional capacity due to hip pain) or pulmonary disease (e.g., chronic obstructive pulmonary disease [COPD]). Similarly, patients during preoperative evaluation may report atypical chest pain or chronic angina for which it may not be straightforward to determine if at baseline or worsening. Another common finding is incidental Q waves or non-specific ST-T segment changes on an electrocardiogram in an asymptomatic patient without a known history of cardiac disease. In these scenarios, clinicians may consider using BNP/NT-proBNP in addition to their clinical evaluation to inform which patients may require further preoperative cardiac investigation of new or atypical symptoms. For example, in a patient with such a clinical presentation and NT-proBNP <100 ng/L, the 30-day perioperative risk would be 1.5% and 0.2% for myocardial infarction and vascular mortality, respectively²⁹; given the very low risk, undergoing surgery without additional preoperative cardiac testing would likely be reasonable. On the contrary, a patient with new shortness of breath and elevated preoperative BNP/NT-proBNP may warrant further investigation, based on the urgency of surgery and patient risk factors. The magnitude of BNP/NT-proBNP elevation may also be factored in, as studies have shown a positive correlation between BNP/NT-proBNP levels and perioperative cardiac complications.²⁹ To our knowledge, formal BNP/NT-proBNP-guided preoperative cardiac testing algorithms have not been studied, but in the authors' clinical experience, preoperative BNP/NT-proBNP can be a useful tool complementing the clinical evaluation to guide preoperative management.

Should BNP/NT-proBNP Be Measured in Patients with Known Cardiac Disease?

In patients with known coronary artery disease or congestive heart failure, BNP/NT-proBNP may be expected to be elevated but can nonetheless be useful to inform on the stability of the disease and refine risk prediction in these higher risk patients. In the VISION NT-proBNP study, among patients with history of coronary artery disease ($n = 1527$), 41.6% had a preoperative NT-proBNP <200 ng/L, and 42.7 and 15.7% had a NT-proBNP of 200 to <1500 ng/L and ≥ 1500 ng/L, respectively.²⁹ Thus, not all patients had a preoperative elevated NT-proBNP and patients with higher levels may indicate a more severe underlying disease or evolving ischemic cardiomyopathy. Similarly, in patients with history of congestive heart disease ($n = 346$), 17.6% had a preoperative NT-proBNP <200 ng/L, 41.9% 200 to <1500 ng/L, and 40.5% ≥ 1500 ng/L. BNP/NT-proBNP levels may also be useful in patients with heart failure with reduced ejection fraction as a comparison with previous levels to assess disease stability. As

discussed above, decision to further investigate preoperatively should be informed by clinical presentation, including signs or symptoms, comorbidities, and risk and urgency of surgery, but elevated BNP/NT-proBNP can help refine discrimination of risk and assess disease severity to guide management.

Chronic Conditions Associated with Elevated Natriuretic Peptides

BNP/NT-proBNP have been studied in a wide array of medical conditions, some of which are relevant in the perioperative setting. Routine preoperative BNP/NT-proBNP screening prior to elective surgery in patients with baseline risk factors can identify undiagnosed or uncontrolled chronic conditions that may require investigation prior to surgery. Knowledge of which conditions can be associated with elevated BNP/NT-proBNP may help guide such decisions. A summary of chronic conditions relevant to the perioperative setting and associated with BNP/NT-proBNP elevation is reported in Table 1.

Hypertension with and without left ventricular hypertrophy

Higher levels of NT-proBNP have been observed in patients with poorly controlled hypertension³⁷ and with left ventricular hypertrophy.³⁸ In both conditions, higher NT-proBNP levels were associated with increased cardiovascular complications at long-term follow-up.

Pulmonary hypertension

In primary pulmonary hypertension, BNP levels have been shown to be elevated with higher levels correlating with worse functional capacity and hemodynamic parameters obtained by right heart catheterization.³⁹

COPD and secondary pulmonary hypertension

Secondary pulmonary hypertension and cor pulmonale are complications seen in COPD patients and associated with poor prognosis.⁴⁰ In the perioperative setting, pulmonary hypertension is associated with significant increase in postoperative morbidity and mortality.⁴¹ Circulatory failure and cardiac arrest following anesthesia induction have been reported in severe case of pulmonary hypertension.⁴² Pulmonary hypertension can be challenging to diagnose clinically but should be suspected in patients with severe COPD. BNP/NT-proBNP has been shown to be significantly elevated in patients with COPD-associated cor pulmonale and to correlate with pulmonary artery pressure.⁴³ In contrast, stable ambulatory COPD patients without heart failure were found to have normal or only mildly elevated natriuretic peptides.⁴³

Table 1. Chronic conditions associated with elevated BNP/NT-proBNP

Conditions	Magnitude of BNP/NT-proBNP elevation
Uncontrolled hypertension	↑
Left ventricular hypertrophy	↑
Clinical hyperthyroidism without ventricular dysfunction	↑
Carcinoid heart disease	↑↑↑
Primary and secondary pulmonary hypertension	↑↑↑
Diastolic dysfunction	↑↑↑
Cor pulmonale	↑↑↑↑↑
End-stage renal disease	↑↑↑↑↑↑
Chronic heart failure	↑↑↑↑↑↑↑

↑ = ≤2–3x upper limit of normal, ↑↑ = 4–5x upper limit of normal, ↑↑↑ = 5–10x upper limit of normal, ↑↑↑↑ = ≥10x upper limit of normal. Ranges for magnitude of BNP/NT-proBNP above the upper limit of normal are approximate estimates based on available literature and may vary depending on clinical presentation. Other conditions not listed in the table may also be associated with elevated BNP/NT-proBNP.

Coronary artery disease

A large body of evidence has also demonstrated the association between BNP/NT-proBNP and coronary artery disease. In the general, non-surgical population, BNP and NT-proBNP have been shown to be associated with long-term cardiovascular outcomes and mortality, independent of cardiovascular risk factors, left ventricular function, and measures of cardiac remodeling.^{44–47} NT-proBNP has also been shown to be correlated with the extent of coronary artery disease and myocardial ischemia in patients with stable angina.^{48–50}

Heart failure

Several studies have demonstrated the diagnostic and prognostic utility of BNP/NT-proBNP in heart failure in the ambulatory setting and acute care setting^{35,51}. In patients with heart failure with preserved ejection fraction, elevated BNP and NT-proBNP independently predicted moderate to severe diastolic dysfunction.⁵² The CCS heart failure guidelines recommend natriuretic peptides screening in the management algorithm of suspected heart failure, with thresholds of BNP >50 ng/L and NT-proBNP >125 ng/L leading to assessment of ventricular function with imaging in the non-operative setting.⁵³

Hyperthyroidism

Thyroid hormones are known to upregulate BNP release and thus elevated BNP/NT-proBNP levels can be found in patients with clinical hyperthyroidism, with and without hyperthyroidism-induced cardiomyopathy.^{54,55}

End-stage kidney disease

BNP and NT-proBNP concentrations have been found to be markedly elevated in patients with end-stage kidney disease

receiving maintenance dialysis, often 20 times the upper limit of both assays.⁵⁶ Some degree of elevation may be due to reduced renal clearance of the proteins, but higher levels remained associated with increased mortality.⁵⁶

Carcinoid heart

Carcinoid heart disease can be found in 20 to 50% of patients with carcinoid syndrome associated with neuroendocrine tumors.⁵⁷ The imaging of choice to detect carcinoid heart disease is echocardiogram but NT-proBNP has value in the diagnostic and prognostic evaluation for carcinoid cardiac involvement.⁵⁸ An NT-proBNP threshold of ≥200 ng/L was associated with 87% sensitivity and 80% specificity for predicting carcinoid heart disease.⁵⁸

Conclusion

Natriuretic peptides are powerful prognostic tools for cardiac complications following noncardiac surgery. It can also be useful in guiding perioperative management, including preoperative cardiac investigation and postoperative surveillance. Several conditions may be associated with elevated BNP/NT-proBNP in the general population undergoing surgery and decision to investigate should consider the patient risk factors, clinical presentation, and indication and urgency of surgery. Further studies on BNP/NT-proBNP-guided preoperative management algorithm and tailored therapy are needed to further inform on this topic.

Learning Points

1. The measurement of preoperative BNP or NT-proBNP adds incremental prognostic value to current clinical risk scores such as the RCRI in the preoperative assessment of select patients (65 years or older, 45–64

- years with significant cardiovascular disease or RCRI score ≥ 1) undergoing inpatient noncardiac surgery.
2. The measurement of preoperative BNP or NT-proBNP is a practical, and reasonable strategy to improve perioperative risk prediction.
3. The measurement of preoperative BNP or NT-proBNP can aid in the discussion of risks associated with elective inpatient noncardiac surgery.
4. BNP or NT-proBNP can be measured as a point-of-care test in the preoperative setting.
5. The measurement of BNP or NT-proBNP may assist in the decision to pursue preoperative investigations for elective inpatient noncardiac surgery.
6. Consider troponin monitoring for 48 to 72 h for patients with an elevated preoperative BNP (≥ 92 ng/L) or NT-proBNP (≥ 300 ng/L)

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