The role of biomarkers and B-type natriuretic peptide in diagnosis and perioperative risk prediction

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Abstract

Biomarkers are important in diagnosis, assessment of disease severity, risk stratification and therapeutic decision-making. Recent studies strongly suggest that there is a role for B-type natriuretic peptide (BtNP) as a powerful prognostic predictor in both the preoperative and postoperative setting. An understanding is required of the specific statistical methodology that is used to assess the value of biomarkers. The main aim of this paper was to discuss the current role that BtNP plays in perioperative risk prediction.

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Introduction

Biomarkers have emerged as important tools, not only for the diagnosis and assessment of disease severity, but also for risk stratification and therapeutic decision-making.[1,2] As an example, cardiac troponins are established biomarkers of myocardial injury with very high sensitivity, and are independently predictive of adverse outcomes following noncardiac surgery.[3] They may be powerful predictors of postoperative major adverse cardiac events (MACE), namely cardiac death and nonfatal myocardial infarction.[3,4] More recently, B-type natriuretic peptide (BtNP) has proven its utility in the nonsurgical setting and in certain centres has been integrated into clinical routine.[1] Several studies have shown that BtNP may serve as a powerful prediction tool in both preoperative risk assessment[5] and postoperative prognostication.[6]

The physiology of BtNP

For any biomarker, it is important to understand the pathophysiology involved in increased synthesis, its physiological effects and its pharmacokinetics.[2]

BtNP, first isolated from porcine brain and hence also called brain-type natriuretic peptide, belongs to the natriuretic peptide family that includes atrial natriuretic peptide (ANP). The major source of BtNP synthesis and secretion is ventricular myocytes and, to a lesser extent, atrial myocardium. ANP is stored in granules in atrial myocytes and released immediately after stimulation. However, minimal BtNP is stored in granules, and rapid gene expression regulates BtNP secretion.[1] BtNP is synthesised as a pre-prohormone comprising 134 amino acids, from which a signal peptide is cleaved to produce pro-brain natriuretic peptide (proBNP), which comprises 108 amino acids. Upon release into the circulation, proBNP is cleaved in a 1:1 ratio into the physiologically active 32-amino acid BNP, which represents the C-terminal fragment, and the biologically inactive 76-amino acid N-terminal fragment [N-terminal pro-brain natriuretic peptide (NT-proBNP)].[1,7,8]

The main stimulus for the release of BtNP is increased myocardial wall stretch mediated by pressure or volume loading. BtNP has been shown to be released in response to myocardial ischaemia,[1] a response that may reflect myocyte stretching in the ischaemic region, rather than ischaemia itself.[8] Angiotensin and endothelin may also stimulate BtNP synthesis and release.[1,8]

The physiological effects of BNP are mediated by its interaction with natriuretic peptide receptor type A (NPR-A), which causes a rise in intracellular cyclic guanosine monophosphate (cGMP).[1] The physiological role of BNP is to counteract the effect of myocyte stretch by causing

peripheral vasodilatation and increasing endothelial permeability. Inhibition of renin and aldosterone production results in natriuresis and diuresis. BNP also inhibits the sympathetic nervous system.[1,8] BNP has a limiting effect on myocardial hypertrophy[8] (the autocrine effect) and fibroblast proliferation (the paracrine effect). On the other hand, ANP is stored in granules and has more rapid endocrine and local effects and a shorter half-life than BNP.

BNP is cleared from plasma by binding to natriuretic peptide receptor type C (NPR-C), and through proteolysis by neutral endopeptidases. BNP and NT-proBNP are cleared in part by the kidneys. NT-proBNP was thought to be more dependent on renal function for its excretion, but recent studies have shown that BNP and NT-proBNP levels rise similarly as creatinine clearance decreases.[1,8] The half-life of BNP is 20 minutes, whereas NT-proBNP has a half-life of 120 minutes. This explains why NT-proBNP serum values are approximately six times higher than BNP values, even though both are released in equimolar proportions. Therefore NT-proBNP has a slightly wider detection range.[1,8]

Studies have shown that NT-proBNP is less sensitive to rapid haemodynamic shifts.[8] NT-proBNP remains stable for 72 hours in whole blood and plasma, whereas BNP assay requires the sample to be kept in ethylenediaminetetraacetic acid (EDTA) and is stable for 24 hours.[8] Owing to the relatively short half-life of both forms of the biomarker, significant alterations in the patient's clinical status may be reflected within 2-12 hours by corresponding changes in BtNP levels.[8]

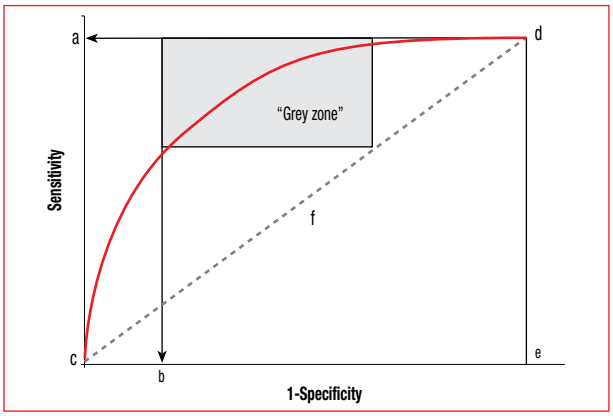
Normal natriuretic peptide levels are difficult to define, as baseline levels are influenced by a number of factors.[1] Levels are lower in men and obese individuals, probably because of sex steroid hormone suppression of BtNP synthesis. Values are higher in elderly patients. Possibly, this relates to myocardial changes that are present prior to the onset of symptoms[1] and to an age-related decline in renal function.[7,8] Patients with anaemia and atrial fibrillation may also have raised levels of BtNP.[7,8]

Statistical analysis in biomarker studies

Sensitivity and specificity, likelihood ratios (LHR), receiver-operating characteristic (ROC) curves and reclassification statistics are among the important statistical indices used to describe the performance of biomarkers. A detailed discussion of these is beyond the scope of this paper.[2,9]

However, two important statistical techniques are applicable to the assessment of the clinical value of biomarkers and warrant emphasis. Firstly, the ROC curve is used to determine an "optimal" cut-off value of the biomarker for disease prediction or outcome. This cut-off attempts to dichotomise the population into two groups that either have, or do not have, the disease. However, clinically, it is more appropriate to propose two cut-offs separated by a "grey zone" (see Figure 1). The first cut-off (a) is a screening test and is chosen to include the diagnosis with near certainty, i.e. privilege sensitivity. The second cut-off (b) is a diagnostic test and is chosen to exclude the diagnosis with near certainty, i.e. privilege specificity. Values within the grey zone are associated with uncertainty, and additional tools, for example clinical, laboratory or imaging, are needed to reach a diagnosis.[2] The area under the ROC curve (AUC) is a measure of the overall accuracy of a test and indicates how well it discriminates between the groups with and without the disease or condition in question. A value of 1 represents a perfect test and a value of 0.5, which corresponds to the identity line (f), represents a test of no predictive value. In general, a value of 0.75-0.9 is considered to be of good diagnostic value.[2]

Secondly a statistical method known as "reclassification statistics" is particularly suited to risk stratification of the grey zone, and it is here that BtNP may have particular utility. The success of the reclassification, by the addition of preoperative BtNP levels, is described by the "net reclassification improvement", which is the difference between the proportion of patients correctly and incorrectly reclassified according to a subsequent adverse outcome.[10] Reclassification statistics should be performed according to a pre-existing risk classification,[10] such as the Revised Cardiac Risk Index (RCRI), which has been adopted by both the American College of Cardiology and the American Heart Association (ACC/AHA) and the European Society of Cardiologists in their proposed cardiovascular evaluation algorithms to determine the clinical utility of a novel biomarker such as BtNP.[11,12]



a: Privilege sensitivity (range 0-1), used as a screening test
b: Privilege specificity, used as a diagnostic test
The area bounded by curved lines (c-d) and solid lines (d-e and e-c): AUC
Dotted line (f): The identity line corresponding to an AUC of 0.5
The grey zone is indicated by the shaded area.

Figure 1: Receiver-operating characteristic (ROC) curve

Clinical applications of BtNP

Heart failure

Evaluation of dyspnoeic patients may be challenging and is associated with a degree of clinical uncertainty.[13] BtNP has been shown to be superior to clinical judgement alone in the diagnosis of acute heart failure.[14,15] Numerous studies have consistently shown that BNP and NT-proBNP levels are elevated in systolic, and more recently, isolated diastolic heart failure. Values correlate directly with disease severity as assessed by New York Heart Association (NYHA) functional class[1,16] (see Figure 2) and inversely with cardiac output.[7]

In systolic heart failure, BtNP levels correlate well with left ventricular end-diastolic and end-systolic volumes, myocardial mass and ejection fraction.[17] In one study that compared the performance of NT-proBNP to echocardiography and cardiac catheterisation, the reliability of NT-proBNP in the diagnosis of isolated diastolic failure was similar to that of tissue Doppler imaging indices (AUC 0.83 vs. 0.81 respectively). NT-proBNP levels correlated strongly with left ventricular filling pressures and had the best negative predictive value (NPV) (94%) of all methods to exclude the diagnosis.[18]

Several studies, in particular two multicentre trials, provide evidence for dual cut-off points in the diagnosis of systolic heart failure (see Table I). The Breathing Not Properly multicentre trial showed that a cut-off value of 100 pg/ml for BNP had a 90% sensitivity, a 76% specificity, an NPV of 90% and an AUC of 0.90.[14] Similarly, the N-terminal pro-BNP Investigation of Dyspnoea in the Emergency Department (PRIDE) study determined that an NT-proBNP value of 300 pg/ml had a sensitivity of 99%, a specificity of 68%, an NPV of 99% and an AUC of 0.94.[15]

BtNP has also been demonstrated to be a strong prognosticator of unfavourable outcome (death, cardiovascular death, readmission or cardiac events) in patients with chronic heart failure or asymptomatic left ventricular dysfunction.[7,19] There is also evidence for the use of BtNP in therapeutic monitoring. Levels are reduced after initiation of medications such as angiotensin-converting enzyme inhibitors or beta blockers.[20] A decrease in levels during initial hospitalisation is associated with a favourable clinical outcome.[21]

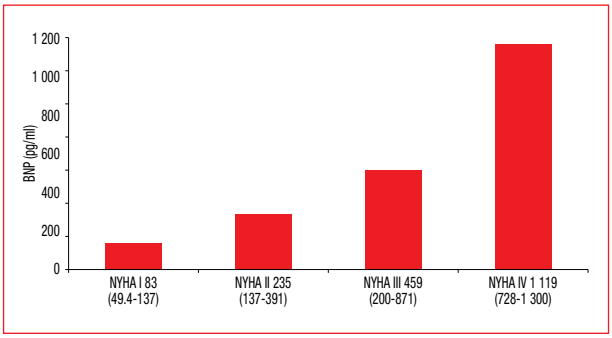


Figure 2: Median (25th and 75th percentiles) BNP levels in patients with heart failure according to NYHA functional status[16]

Ischaemic heart disease

Following myocardial infarction, the rise in BtNP is closely linked to the degree of myocardial damage and correlates well with left ventricular ejection fraction.[8] However, BtNP will not replace troponins as a means of diagnosis, as the latter is more sensitive and specific with a stronger LHR. However, BtNP has shown superiority to troponins in the prediction of overall short-term (< 30 days) and long-term (< 51 months) mortality.[8]

Cardiac disease in pregnancy

Early recognition of a deterioration in maternal cardiac status is important to ensure good maternal and foetal outcome. Pregnancy itself can mimic the symptoms and signs of cardiac decompensation. BtNP may offer a more widely available early marker of worsening cardiac disease.[22] A recent prospective observational study compared serial BNP levels in parturients with congenital or acquired cardiac disease with those in healthy pregnant controls. Patients with left ventricular dysfunction (ejection fraction < 55%) had significantly higher BNP levels than healthy parturients. An important finding of this study was that BNP levels less than 100 pg/ml had an almost 100% NPV for adverse maternal cardiac events.[22]

Levels of NT-proBNP have been shown to be significantly higher in patients with pre-eclampsia compared with those in normotensive pregnant controls. Kale et al observed that the median serum NT-proBNP level was 430 ±29 pg/ml in pre-eclampsia, compared with 74 ±17 pg/ml in normotensive pregnant women (p-value < 0.001). This was postulated to be because of elevated left ventricular filling pressures and the presence of underlying left ventricular diastolic dysfunction.[23] Resnik et al confirmed these findings. They found that normal pregnancy was associated with a median BNP level of less than 20 pg/ml, and that a BNP cut-off of

Table I: Cut-off values of BNP and NT-proBNP for the diagnosis of heart failure in patients presenting with dyspnoea[14,15]

	Rule-out, i.e. heart failure is unlikely	Rule-in, i.e. heart failure is likely
BNP (pg/ml)	100	500
NT-proBNP (pg/ml), age < 50 years	300	450
NT-proBNP (pg/ml), age > 50 years	300	900

less than 40.6 pg/ml had a negative predictive value of 92% in excluding a diagnosis of pre-eclampsia.[24] This was based on BNP levels taken in patients with mild and severe pre-eclampsia in all three trimesters.

BtNP in the perioperative setting

NT-proBNP may be preferred to BNP owing to the longer half-life of the former and a lower susceptibility to the rapid haemodynamic changes associated with anaesthesia and surgery.[25] However, both markers appear to correlate similarly with clinical status and either may be used perioperatively.

Cardiac surgery

In patients with aortic stenosis, BNP and NT-proBNP levels not only correlate with disease severity, but also decline after successful valve replacement. Further larger studies are warranted to determine the role of BtNP in the diagnosis, prognosis and management of patients with valvular heart disease.[1]

Preoperative BtNP levels have been shown to correlate with long-term outcome in patients undergoing coronary artery surgery.[26] Fellahi et al have demonstrated that after cardiac surgery, simultaneous measurement of BNP, cardiac troponins and C-reactive protein (CRP) improves the prediction of long-term outcome when compared with the European System for Cardiac Operative Risk Evaluation (euroSCORE).[25] Theoretically, these biomarkers test different pathological processes. BNP reflects cardiac strain, troponins reflect myocardial necrosis, and CRP represents the inflammatory response, all of which presumably influence final outcome after cardiac surgery.[25]

Noncardiac surgery

Similarly, Choi et al reported that after noncardiac surgery, the prediction of MACE by RCRI was significantly improved by the addition of the biomarkers CRP and NT-proBNP. If the RCRI score was ≥ 2, the AUC for the prediction of MACE increased from 0.59 to 0.77, when combined with a CRP of greater than 3.4 mg/l and an NT-proBNP of greater than 301 ng/l.[27]

A 2009 meta-analysis assessed the prognostic value of elevated BtNP levels in predicting mortality and MACE, by evaluating 15 studies with almost 5 000 patients.[5] The authors concluded that preoperative BNP and NT-proBNP elevation was associated with a greatly increased risk of adverse outcome. The odds ratio for short-term MACE was 19.77 [95% confidence interval (CI): 13.18-29.65, p-value < 0.0001], 9.28 (95% CI: 3.51-24.56, p-value < 0.0001) for all-cause mortality, and 23.88 (95% CI: 9.43-60.43, p-value < 0.00001) for cardiac death.[5]

Mahla et al identified a postoperative NT-proBNP level of > 860 pg/ml (95% CI: 556-1 054 pg/ml) to be strongly predictive of adverse in-hospital and long-term cardiac outcome.[6] This value of NT-proBNP is similar to that in nonsurgical patients who are diagnosed with heart failure.[15] It is postulated that these adverse outcomes are a result of incorporating dynamic intraoperative and postoperative stress exposure.

This study is important, since early recognition of prolonged postoperative ischaemia or heart failure is challenging in routine clinical practice. Ischaemia often presents silently in this period and coexistent dyspnoea may be of pulmonary origin.[6] Postoperative NT-proBNP levels may help to guide early therapeutic decisions in patients without postoperative troponin elevation or leak.[28-31]

Implications for perioperative risk assessment and risk stratification

At this point, it is instructive to consider the aspects of a biomarker that are important in determining its clinical value:[2]

- The level of the biomarker should be significantly increased in diseased patients, when compared with controls.
- These diagnostic properties should aid decision-making and shorten the time to reach a diagnosis.
- The technical aspects of the biomarker test should be assessed. These include cost, invasiveness, difficulty in performance and rapidity of obtaining the result. The utility of the test should then be considered in the context of the prevalence and burden of the disease in question.
- Optimally, the use of the biomarker should be shown to influence outcome in intervention studies.

The RCRI of Lee et al has been accepted by the ACC/AHA as a validated scoring system to predict cardiac risk in noncardiac surgery.[32] However, in a recent individual patient data meta-analysis of studies on patients undergoing vascular surgery, Rodseth et al demonstrated the modest performance of this clinical scoring system. The RCRI AUC for the prediction of MACE and for all-cause mortality was 61.6% (95% CI, 54.6-68.6%) and 65.8% (95% CI, 55.7-75.9%), respectively, which was significantly lower than the AUC for BNP at 80.5% (95% CI, 75.1-85.8%).[33]

The RCRI only meets the criteria for a clinically useful test when a patient has no clinical risk factors (a negative LHR of 0.16).[34,35] The discrimination was found to be poor, with a positive LHR of 2.7 and 4.8 in patients with either two, or three or more risk factors, respectively.[34] In addition, the RCRI is not an objective index.[35] The five clinical predictors are equally weighted, which may not be appropriate in terms of impact on overall risk, and they do not reflect the severity of the predictor in the individual patient.

The lack of predictive value of the RCRI emphasises the need for a reliable, objective screening test with a strong predictive power, such as BtNP, to stratify patients at risk of perioperative cardiac morbidity and mortality. However, the problem faced by perioperative clinicians is identification of appropriate cut-off values that are applicable to the perioperative setting. The meta-analysis by Rodseth et al set out to achieve this objective.[33]

Individual patient data were obtained for over 800 vascular surgery patients who were followed up for 30 days postoperatively. The primary end-point was postoperative MACE. The first cut-off identified for BNP was 30 pg/ml. This was a screening test with 95% sensitivity. The second cut-off, with a value of 116 pg/ml, was the general optimal test, the point on the ROC curve with the highest rate of true positive and the lowest rate of false positive results. The third cut-off of 372 pg/ml was determined for a diagnostic test with a 95% specificity for MACE. As a continuum in predicting MACE, the AUC for BNP was 80.5% (95% CI, 75.1-85.8%).[33]

In this meta-analysis, all patients were classified according to the RCRI into low-, intermediate- or high-risk categories. Patients were then reclassified using the added information provided by their BNP level. If the BNP level was above the optimal cut-off, they were moved up one risk category, and if the level was less than the optimal cut-off, they were moved down one category. The addition of BNP to the RCRI resulted in a statistically significant ($z = 5.48$, p-value < 0.001) improvement of its predictive performance and discrimination, with a net reclassification improvement of 58%.[33] Interestingly, the majority of procedures that were performed were infrainguinal and the incidence of MACE was as high as 36.7% in the group with BNP levels above the diagnostic cut-off of 372 pg/ml.

ACC/AHA guidelines suggest that once high-risk patients have been identified and intermediate- to high-risk surgery is anticipated, noninvasive cardiac testing should be performed.[11] However, the dynamic tests of inducible ischaemia (dobutamine or dipyridamole stress echocardiography) tend to have strong NPVs and low negative LHRs,[36] and therefore have greater value in identifying patients who are unlikely to have an adverse event than those with a likely poor outcome.[36,37] This lack of accuracy in predicting adverse outcome in the setting of patients with ischaemic heart disease may be because of the interplay of various factors, such as oxygen supply-demand balance, inflammation, hypercoagulability and shear stress, that are implicated in perioperative myocardial infarction. Risk stratification, using BtNP, may circumvent some of the limitations of these noninvasive tests of cardiac function in predicting adverse outcome. The study by Rodseth et al suggests that BNP levels below the screening cut-off could obviate the need for further cardiac investigations, while levels above the optimal cut-off, and certainly above the diagnostic cut-off, could indicate investigations to assess left ventricular dysfunction and/or inducible ischaemia.[33,38] Large and adequately powered studies that compare the performance of BtNP to noninvasive tests and imaging studies are needed to test this hypothesis.[6] Depending upon the outcomes of such investigations, BtNP risk stratification could influence the perioperative process by altering the level of perioperative monitoring and surveillance. Furthermore, high-risk patients could be offered more conservative surgery or medical therapy.[8]

Conclusion

A growing body of evidence supports the use of BtNP in the perioperative diagnosis, risk assessment and prognostication of cardiac and noncardiac surgical patients, as well as obstetric patients with cardiac disease. Considerable research is required to assess whether the perioperative measurement of BtNP levels influences patient outcome.

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