B type natriuretic peptide – a diagnostic breakthrough in peri-operative cardiac risk assessment?

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Summary
The B-type natriuretic peptides; B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide, are increasing being used as biomarkers for the diagnosis, management and prognostication of cardiac failure, but their application in the peri-operative period is unclear. This review examines the current understanding of the role of B-type natriuretic peptides in both the operative and non-operative settings. Normal values, diagnostic thresholds, monitoring targets and significant prognostic levels are identified. Using this as a background, the role of B-type natriuretic peptides in the prediction of peri-operative mortality and morbidity is examined and potential confounders, such as renal failure and body mass index, which may impact significantly on the utility of the biomarkers, are discussed. Clinical recommendations with regard to its use are made and a research agenda is proposed for future peri-operative studies.

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Anaesthetists have traditionally attempted to improve peri-operative outcomes by focusing on the diagnosis, prevention and treatment of myocardial ischaemia in high-risk surgical patients, with limited success [1–5]. This focus may be due to the ability to readily monitor, diagnose and treat ischaemia. However, congestive cardiac failure, despite its inclusion in most clinical cardiac risk scores and associated morbidity and mortality, is a relatively neglected predictor and treatment target with respect to peri-operative morbidity and mortality [6–10]. This may be because of difficulty in clinically diagnosing degrees of cardiac failure and monitoring its response to treatment [11, 12]. The importance of cardiac failure in the peri-operative period has been highlighted by studies showing it to be associated with a higher risk-adjusted operative mortality than the diagnosis of coronary artery disease (11.7% vs 6.6%, p < 0.001) [7].

B-type natriuretic peptide (BtNP), comprising B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), are increasingly being used for the diagnosis, management and prognostication of cardiac failure [13, 14]. The role of BtNP in the peri-operative period has not been well defined. Potential confounders such as age, sex, renal failure and body mass index (BMI) may affect the performance of these biomarkers and need to be taken into account when proposing clinical recommendations for their utilisation and directions for further research.

Physiology of B-type natriuretic peptide
The natriuretic peptide system
BNP is a hormone secreted by cardiac myocytes in response to mechanical stretch. It forms part of a family of natriuretic peptides, which also consist of atrial natriuretic peptides (ANP), secreted from atrial tissue, and C-type natriuretic peptides (CNP) secreted primarily from the vascular endothelium. These peptides share a common structure and respond to volume overload of the vasculature to maintain homeostasis. They may be thought of as a counter-regulatory system for the renin-angiotensin system [15–17].

BNP production, function and clearance
BNP is formed as a pre-prohormone, which is split to form proBNP. ProBNP is further broken down to the active hormone BNP_{1-32} and a breakdown product NT-pro-BNP. Once proBNP has been synthesised,
variable amounts of BNP_{1-32}, NT-proBNP and proBNP itself, are released into the circulation. BNP_{1-32} rapidly undergoes breakdown to form biologically active BNP fragments; BNP_{3-32} and BNP_{7-32}. BNP is primarily produced by cardiac myocytes and fibroblasts. The atria produce both BNP and ANP [18, 19]. The primary stimulus for production is myocyte stretch mediated by both pressure and volume, with hypoxia being more recently identified as a stimulus [20–22]. It is important to note that the rise in BNP due to hypoxia may reflect myocyte stretching in the hypoxic region rather than hypoxia per se, and that its production is modulated by other neurohormones such as angiotensin and endothelin [20, 23]. During periods of cardiac strain, up regulation of BNP production occurs with levels of BNP reflecting clinical significant change within 2–12 h [24]. BNP production occurs more rapidly and extensively in the ventricle than in the atria, resulting in a greater degree of ventricular secreted BNP relative to that of the atria [25].

The physiological role of BNP is to effect an adaptive response to cardiovascular strain. It modulates the cardiovascular system by limiting myocardial hypertrophy, causing peripheral vasodilatation and increasing endothelial permeability. At a renal level, inhibition of renin and aldosterone production occurs, with resulting natriuresis and diuresis. In the central nervous system the inhibition of salt and water intake, in addition to vasopressin secretion, is facilitated [26]. These effects are mediated through natriuretic peptide receptors A and B [27]. Type C receptors, together with neutral endopeptidases, act as scavengers and clear the peptides from the circulation [23]. Attempts to utilise the actions of natriuretic peptides pharmacologically have resulted in the development of natriuretic peptide analogues such as anaritide and nesiritide, and neutral endopeptidase inhibitors such as candoxatrilat. These have been used in the treatment of renal failure and congestive cardiac failure with varying degrees of success [28–33].

BNP are cleared in part by the kidney and thus levels rise as renal function deteriorates [34]. Based on early investigations it has been commonly accepted that the plasma clearance of NT-pro-BNP is more dependant on renal function than BNP [35, 36]. This may have been related to technical errors in the detection of BNP levels and the use of univariable correlation coefficients during data analysis. More recently it has been demonstrated that BNP and NT-pro-BNP correlate well ($r = 0.91; p < 0.01$) when examined across the spectrum of renal disease and that no clear difference can be shown in chronic renal disease [34, 37]. For each $30 \text{ ml.min}^{-1}$ reduction in creatinine clearance, from $150 \text{ ml.min}^{-1}$ to $30 \text{ ml.min}^{-1}$, BNP increased by 9%, 22%, 44% and 89% and NT-pro-BNP increased by 9%, 24%, 46% and 95% respectively [34].

Normal natriuretic peptide levels

Normal BtNP levels have not been well defined, but the ranges shown in Table 1 have been suggested for clinical use [38–40].

There are multiple factors that influence the normal values of BtNP. Males have consistently lower levels than females, probably due to androgen suppression of pro-BNP synthesis [41]. A higher body mass index results in lower normal values of BtNP, the mechanism of which is unclear, but may be related to increased clearance [42, 43]. More recently it has been postulated that sex steroid hormones produced in lean mass may suppress natriuretic peptide synthesis or increase its clearance by releasing neutral endopeptidases from cardiac myocytes [44]. As previously discussed, renal failure has a significant impact on natriuretic peptides resulting in higher normal values.

Table 1  Normal age adjusted ranges of BNP and NT-pro-BNP.

<table>
<thead>
<tr>
<th>Patient age</th>
<th>BNP</th>
<th>NT-pro-BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young adults</td>
<td>&lt; 25 pg.ml$^{-1}$ [38]</td>
<td>&lt; 70 pg.ml$^{-1}$ [38]</td>
</tr>
<tr>
<td>45–59 years</td>
<td>&lt; 100 pg.ml$^{-1}$ – males</td>
<td>&lt; 164 pg.ml$^{-1}$ – females [39]</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>&lt; 98 pg.ml$^{-1}$ [40]</td>
<td>&lt; 172 pg.ml$^{-1}$ – males</td>
</tr>
<tr>
<td></td>
<td>&lt; 225 pg.ml$^{-1}$ – females [39]</td>
<td></td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; NT-pro-BNP, N-terminal pro-B type natriuretic peptide.

Clinical range: BNP 0–5000 pg.ml$^{-1}$; NT-pro-BNP 0–35 000 pg.ml$^{-1}$.

BtNP in medical disease

BtNP and cardiac failure

The close association of BtNP levels with myocardial stress and its expression in cardiac failure has resulted in its development as a biomarker of cardiac failure. Levels are directly related to left ventricular mass and inversely related to left ventricular ejection fraction [45–48].

The choice whether to monitor BNP or NT-pro-BNP remains unclear. BNP demonstrates a shorter half-life of approximately 20 min in contrast to NT-pro-BNP’s half-life of 1–2 h. NT-pro-BNP has a slightly wider detection range and a more stable structure compared to BNP [49]. Thus NT-pro-BNP levels may be less sensitive to rapid haemodynamic shifts [50–52]. Good clinical correlation between the two hormones has been shown, and both markers perform well when prognosticating, although NT-pro-BNP may be superior to BNP for predicting mortality, morbidity, hospitalisation for cardiac failure, left ventricular dysfunction and coronary artery disease [53–55]. This may be due to its decreased sensitivity to...
rapid haemodynamic fluctuation, its precision over a wide range (30–35 000 pg.ml⁻¹), and its greater stability in plasma [24].

BtNP has been extensively used in the emergency room as a tool to identify cardiac failure in the clinical scenario of acute dyspnoea. NT-pro-BNP has shown to be superior to clinical judgement in the diagnosis of acute cardiac failure (receiver operating characteristics curve (ROC) 0.94 vs ROC 0.90, p = 0.006) and when used in combination with clinical judgement further improved diagnostic sensitivity and specificity (ROC 0.96). The combination performed significantly better than NT-pro-BNP (p = 0.04) and clinical judgement (p < 0.0001) in isolation. The use of NT-pro-BNP together with clinical assessment of patients resulted in improved management, with a reduction in time spent in the emergency department (6.3–5.6 h; p = 0.031) and a reduction in the number of patients rehospitalised over 60 days by 35% (51–33; p = 0.046) [56].

A BNP level of 100 pg.ml⁻¹ has been identified as the optimal cut-off point to differentiate cardiac failure from other causes of dyspnoea (90% sensitivity, 76% specificity), and a level > 400 pg.ml⁻¹ has been proposed as a cut-off point based on a positive likelihood greater than 10 in diagnosing cardiac failure [57–60]. When considering NT-pro-BNP for the diagnosis of cardiac failure, the use of dual cut-off points, with an exclusion level < 300 pg.ml⁻¹ (98% negative predictive value) and an inclusion level > 900 pg.ml⁻¹ (76% positive predictive value), resulted in further improved diagnostic ability [61].

This raises the issue of how to handle patients who fall in the intermediate or grey zone with BNP levels between 100 to 400 pg.ml⁻¹ or NT-pro-BNP levels between 300 to 900 pg.ml⁻¹. BtNP levels should be regarded as a continuous variable, with even mildly elevated levels being associated with increased risk of death, heart failure, atrial fibrillation and stroke [62, 63]. Those falling in the grey zone have an increased mortality risk in comparison to those below the cut-off levels, irrespective of the cause of the increase in BtNP [64]. The second point to consider is that there are many possible causes of an elevated BtNP level other than congestive cardiac failure. Table 2 presents a list of non cardiac failure causes of an elevated BNP level [64, 133–135].

Table 2 Non cardiac failure causes of raised BtNP [64, 133–135].

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart muscle disease</td>
<td>Pneumonia / bronchitis</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Acute cardiomyopathy</td>
<td>Chronic obstructive</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Pulmonary disease</td>
<td>tract pathology</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Lung carcinoma</td>
<td>Cancer</td>
</tr>
<tr>
<td>cardiomyopathy</td>
<td>Pulmonary embolism</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Pulmonary hypertension</td>
<td>Septic shock</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Acute respiratory</td>
<td>Burns</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>distress syndrome</td>
<td>Ischaemia stroke</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td>Sleep apnoea</td>
</tr>
<tr>
<td>Pericarditis</td>
<td></td>
<td>Hyperthyroidism</td>
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<tr>
<td>Valvular heart disease</td>
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</tr>
</tbody>
</table>

BtNP, B-type natriuretic peptides.

differential diagnosis of a raised BtNP will assist the clinician in making an accurate diagnosis.

Age is a vital variable to take into consideration when interpreting BtNP, as normal values of BtNP increase with increasing age. This is most probably due to age-related changes in the ventricle, subclinical cardiac dysfunction and decreases in renal function [65–67]. The effect of ageing on normal reference values can be seen in the progression of the 95th percentile reference limit for BNP increasing from 40 pg.ml⁻¹ in age 55–64 years (sensitivity 80%, specificity 95%) to 86 pg.ml⁻¹ in patient’s age ≥ 75 years (sensitivity 89%, specificity 62%) [67]. To retain specificity in the diagnosis of congestive cardiac failure, age stratified levels have been suggested (Table 3). Their use was able to improve the positive predictive value from 79% to 88% without an overall loss of sensitivity of specificity, and decreased the number of patients falling into the grey zone from 26% to 16% [68, 69].

In patients with chronic cardiac failure BtNP has been used to monitor disease progression, as well as to prognosticate across the entire spectrum of disease severity. A single NT-pro-BNP level taken from a patient with cardiac failure has been shown to accurately

Table 3 BtNP levels for the diagnosis of cardiac failure.

<table>
<thead>
<tr>
<th>Acute heart failure BNP</th>
<th>NT-pro-BNP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>&gt; 400 pg.ml⁻¹ [57]</td>
</tr>
<tr>
<td></td>
<td>50–75 years – &gt; 900 pg.ml⁻¹</td>
</tr>
<tr>
<td></td>
<td>Severe chronic renal failure and</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 years – &gt; 1200 pg.ml⁻¹ [124]</td>
</tr>
<tr>
<td>Exclusion</td>
<td>&lt; 100 pg.ml⁻¹ [58]</td>
</tr>
</tbody>
</table>

BtNP, B-type natriuretic peptides; BNP, B-type natriuretic peptide; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.
predict both mortality and subsequent hospitalisation. In 5010 patients with mild to moderate cardiac failure, for each 500 pg.ml\(^{-1}\) NT-proBNP above baseline there was an increased mortality risk of 3.8% \( (p < 0.0001) \) [54]. A systematic review has similarly found that the relative risk of death increases by 35% for each 100 pg.ml\(^{-1}\) increase of BNP (95% CI, 22–49%; \( p = 0.096 \)) over a period of 1.5–3 years [70].

The response to treatment can be monitored by a change in BNP levels, with the initiation of diuretic, angiotensin converting enzyme inhibitor (ACEI) or vasodilator therapy resulting in a measurable decrease in levels, and their withdrawal resulting in increases [71].

**NT-pro-BNP further allows the titration of therapy to achieve a maximal individual response by targeting specific levels [72, 73].**

**BtNP and cardiac ischaemia**

A rise in BNP is closely linked to the degree of myocardial damage sustained during the period of ischaemia with large amounts of cardiac muscle damage resulting in significant rises in BNP levels [74, 75]. Following acute myocardial infarction, BNP levels correlate with left ventricular ejection fraction \( (r = -0.63, p < 0.0001) \) and are higher in patients in whom remodelling occurs \( (195 \, \text{pg.ml}^{-1} \text{ vs } 320 \, \text{pg.ml}^{-1}; \ p = 0.010) \) [76, 77]. In the subset of patients presenting with symptoms of acute coronary syndrome without clinical evidence of heart failure, BNP levels were statistically different \( (p < 0.0001) \) between those with acute myocardial infarction \( \text{median 203.5 pg.ml}^{-1} \), unstable angina \( (77.9 \, \text{pg.ml}^{-1}) \) and patients without acute coronary syndrome (ACS) \( (27.7 \, \text{pg.ml}^{-1}) \) [78]. Despite BNP being significantly more sensitive in the diagnosis of non-ST segment myocardial infarction than troponin-I \( (70.8\% \text{ vs } 50.7\%, \ 95\% \text{ CI}, \ p < 0.0001) \) its relatively low positive \( (2.28) \) and negative \( (0.42) \) likelihood ratios do not allow its use as a replacement for troponin-I [78]. The combination of BNP and troponins may have utility in ruling out chest pain of cardiac origin [79]. It must be emphasised that, in the presence of cardiac failure symptoms, absolute levels of BNP were not able to identify those who had acute myocardial infarction from those that did not [78].

NT-pro-BNP is more useful in prognosticating in the patient with ACS where a single measurement of NT-pro-BNP on admission is able to stratify risk of death in both the short term \( (< 30 \text{ days}) \) and long term \( (> 30 \text{ days to 51 months}) \) [80–82]. When compared to troponin T and C-reactive protein, NT-pro-BNP was superior in predicting mortality and its predictive value increased exponentially across the whole spectrum of NT-pro-BNP levels, with a rate of 0.4% in the lower decile \( (\leq 98 \, \text{pg.ml}^{-1}) \) and 27.1% in the highest decile \( (> 4634 \, \text{pg.ml}^{-1}) \) [83]. In non-ST-segment elevation myocardial infarction, there was no relationship between NT-pro-BNP and infarct mass or relative infarct size, and no relationship between cardiac troponins and left ventricular ejection fractions. This suggests that NT-pro-BNP retains a predilection towards a better performance for estimation of left ventricular ejection fractions than infarct size, where cardiac troponins remain superior [84].

Patients with higher levels of NT-pro-BNP may benefit from early identification and subsequent revascularization. Patients in the third NT-pro-BNP tertile showed a 7.3% reduction in mortality \( (\text{risk ratio 0.46, 95\% CI, 0.21–1.00}) \) and similarly patients with NT-pro-BNP elevations \( \geq 237 \, \text{pg.ml}^{-1} \) were observed to have a lower mortality following revascularization \( (7.0\% \text{ vs } 2.7\% \) [83, 85]). BtNP has also been used to successfully prognosticate long-term outcomes in patients with stable coronary artery disease (CAD) [86, 87].

**BtNP and screening for cardiac disease**

While BtNP have been used to identify overt cardiac pathology, there has been much interest in their use to detect subclinical ventricular dysfunction [53]. It is possible to screen for a large group of cardiovascular pathologies including atrial fibrillation, pulmonary hypertension, valvular heart disease and diastolic ventricular dysfunction [39, 88–90]. Although cost may be prohibitive for mass screening, BtNP may have a role in identifying high risk patients who require referral for echocardiography or to cardiac specialists, a strategy that has been shown to be cost-effective when compared to screening by ECG [91, 92]. Natriuretic peptides are now being considered as a screening tool for use by the life insurance industry [93].

**BtNP in intensive care**

The role of BNP in intensive care medicine will not be dealt with in detail in this review save to say that after its initial over expression in patients with sepsis it has been found to function well as an independent prognostic marker of mortality in severe sepsis. Its primary role may lie in identifying patients with cardiac injury and dysfunction [94, 95]. The interested reader is referred to reviews by Phua and Omland for an overview of its role in critical care medicine [96, 97].

**BNP in anaesthesia**

The traditional model of the pathophysiology surrounding peri-operative cardiac events has focused on the classic supply/demand ischaemia hypothesis, and the concept of the vulnerable plaque, blood and myocardium as related to ACS [5, 98]. The concept of the myocardium at risk of
failure, due to increased metabolic demand has not been explored. With a risk-adjusted operative mortality of 11.7% and a risk adjusted 30-day readmission rate of 20% in patients diagnosed with cardiac failure, significantly higher than the 6.6% and 14.2% for patients with CAD (p < 0.001), it is increasingly being recognised that there is significant mortality and morbidity associated with the diagnosis of cardiac failure [6, 7].

Utility of BNP levels in non-cardiac surgery

The ability of BNP to diagnose and prognosticate in patients with cardiac failure has generated a great amount of interest in its potential use in prognosticating for cardiac outcomes in the peri-operative period.

Pre-operative BNP levels

Most of the studies that have been conducted thus far have looked at determining optimal cut-off points for predicting postoperative cardiac events; cardiac death, non-fatal myocardial infarction, heart failure, acute pulmonary oedema and haemodynamic compromise from cardiac arrhythmias, as well as composites of the above [63, 99–110]. The study characteristics are shown in Table 4.

Interestingly in one cohort 36 patients with levels > 460 pg.ml⁻¹, who were not included in the study, had their surgery cancelled as a direct result of their elevated levels. These patients would fulfil the BNP diagnostic criteria for cardiac failure [57]. In 10% of patients, adjustments were made to medications and in 4% of patients, arrangements were made to follow up with their cardiology service. Although the outcomes of these patients were not independently analysed from the rest of the group, this serves as an example of how the use of BNP may impact on peri-operative management [59, 60, 99].

A BNP above the level of 40 pg.ml⁻¹ was shown to be associated with a five-fold increase in the risk of developing new ECG abnormalities or a raised post-operative cardiac troponin [102]. A meta-analysis of the use of BNP in predicting 30-day major adverse cardiac outcomes in vascular surgery, found the test to have a sensitivity of 83% and a specificity of 73% with a positive likelihood ratio of 3.1 and a negative likelihood ratio of 0.23 [110].

How should these wildly divergent discriminatory thresholds be interpreted? Variations in patient cohorts with respect to age, gender, co-morbidity, BMI and degree of pre-existing cardiac failure probably make attempts to define a single universally applicable BNP discrimination point an exercise in futility. The optimal discrimination point will be a factor of the prevalence of cardiac pathology in the population being examined. Groups with high numbers of patients with cardiac dysfunction will have high median BNP levels, which will result in higher discrimination points. This is shown in the study cohort by Cuthbertson where one cohort of patients undergoing emergency surgery, with a median BNP of 100 pg.ml⁻¹, resulted in an optimal discrimination threshold of 170 pg.ml⁻¹. The second cohort of patients undergoing elective major non-cardiac surgery, with a median BNP of 26.6 pg.ml⁻¹, resulted in an optimal discrimination threshold of 40 pg.ml⁻¹ [102, 103].

In addition, the period of observation for each study influences the derived threshold, with the threshold decreasing as the event horizon is extended. Patients with

Table 4 Characteristics of studies examining the peri-operative role of BNP in non cardiac surgery.

<table>
<thead>
<tr>
<th>First author</th>
<th>Surgery</th>
<th>Urgency of surgery</th>
<th>Study period</th>
<th>Patient numbers</th>
<th>Optimal discrimination point</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dernilis [99]</td>
<td>Mixed vascular / non vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>1590</td>
<td>189 pg.ml⁻¹</td>
</tr>
<tr>
<td>Cuthbertson [103]</td>
<td>Mixed vascular / non vascular</td>
<td>Emergency</td>
<td>6 months (emergency surgery)</td>
<td>40</td>
<td>170 pg.ml⁻¹</td>
</tr>
<tr>
<td>Leibowitz [109]</td>
<td>Non vascular</td>
<td>Mixed elective / emergency</td>
<td>Short term &lt; 30 days</td>
<td>44</td>
<td>165 pg.ml⁻¹</td>
</tr>
<tr>
<td>Gibson [101]</td>
<td>Mixed vascular / non vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>190</td>
<td>108.5 pg.ml⁻¹</td>
</tr>
<tr>
<td>Cuthbertson [102]</td>
<td>Mixed vascular / non vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>204</td>
<td>40 pg.ml⁻¹</td>
</tr>
<tr>
<td>Cuthbertson [63]</td>
<td>Mixed vascular / non vascular</td>
<td>Elective</td>
<td>Median 654 days</td>
<td>204</td>
<td>35 pg.ml⁻¹</td>
</tr>
<tr>
<td>NT-pro-BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feringa [105]</td>
<td>Vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>170</td>
<td>533 pg.ml⁻¹</td>
</tr>
<tr>
<td>Goel [108]</td>
<td>Vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>356</td>
<td>478 pg.ml⁻¹</td>
</tr>
<tr>
<td>Yeh [100]</td>
<td>Mixed vascular / non vascular</td>
<td>Elective</td>
<td>Short term &lt; 30 days</td>
<td>190</td>
<td>450 pg.ml⁻¹</td>
</tr>
<tr>
<td>Feringa [106]</td>
<td>Vascular</td>
<td>Elective</td>
<td>14 months</td>
<td>335</td>
<td>319 pg.ml⁻¹</td>
</tr>
<tr>
<td>Mahla [107]</td>
<td>Vascular</td>
<td>Elective</td>
<td>Median 826 days</td>
<td>218</td>
<td>280 pg.ml⁻¹</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptides; BNP, B-type natriuretic peptide; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.
high levels of BtNP have events earlier in their observation periods resulting in higher thresholds. This can be seen in the studies by Cuthbertson et al., where the BNP threshold decreased from 40 pg.ml$^{-1}$, when observed up to 3 days postoperatively, to 35 pg.ml$^{-1}$ when followed up to a median of 654 days [63, 102]. In the Feringa cohort, who used NT-pro-BNP, the threshold decreased from 533–319 pg.ml$^{-1}$ when the follow-up period was extended from 30 days to a median of 14 months [105, 106].

What is clear from these studies is that there is a direct association between increasing levels of BtNP and risk of postoperative cardiac events. As BtNP levels rise so does the risk of postoperative cardiac events, including cardiac death, non-fatal myocardial infarction, acute pulmonary oedema and cardiac arrhythmias, and the earlier in the postoperative period these events will occur [99]. In addition, as has been shown by Cuthbertson et al., even small deviations (≥ 35 pg.ml$^{-1}$) from normal increase the risk of cardiac events [63].

**Postoperative BNP levels**

Of particular interest is the single study that examined the role of postoperative NT-pro-BNP in predicting mortality and morbidity [107]. This is the first study to extend the role of BtNP beyond that of pre-operative risk prediction by examining the prognostic ability of a level drawn in the postoperative period. Mahla et al. identified a greater rise in postoperative NT-pro-BNP in those patients who sustained a cardiovascular event compared to those who did not (609 vs 183 pg.ml$^{-1}$; p < 0.001). An optimal postoperative discrimination threshold of 860 pg.ml$^{-1}$ (sensitivity 73%, specificity 71%) for the prediction of postoperative cardiovascular events was derived.

**Cardiac surgery**

In the pre-operative scenario it has been suggested that BNP levels may be useful in identifying the optimal time for surgical intervention in asymptomatic or mildly symptomatic patients with valvular heart disease [111]. By multivariate analysis, NT-pro-BNP has been shown to independently predict postoperative survival in patients with severe aortic stenosis (p < 0.001) [112]. Concentrations have been shown to correlate well with the euroSCORE ($r = 0.958$; p < 0.001) and to predict 1-year mortality. Patients with high levels spent more time in ICU, required more inotropic support, and developed more renal failure than those with low levels, reflecting temporary ventricular dysfunction [113–115]. In comparison to patients with BNP levels in the first quartile, the odds ratio for developing postoperative atrial fibrillation increased to 3.7 (95% CI 1.15–11.9, P$_{trend} = 0.03$) for patients in the highest quartile [116].

**Clinical recommendations**

In patients with subclinical cardiac failure the use of BNP to identify patients with ejection fractions ≤50% or mild diastolic dysfunction consistently resulted in an area under the curve < 0.70, insufficient to be used as a screening test [89]. The implication of this finding in the perioperative setting is that it is clearly not useful or cost effective for every patient to have a pre-operative BtNP done. The use of clinical risk factors will identify higher risk patients who would benefit from pre-operative testing. The existing AHA/ACC guidelines on perioperative cardiovascular evaluation and management for non cardiac surgery provide a structure around which to guide the use of BtNP. The sequential steps in the algorithm; active cardiac conditions, low risk surgeries, functional capacity and clinical risk stratification, are discussed in relation to the use of BtNP [1].

As has been shown in this review BtNP has a role to play in most of the disease processes defined as active cardiac conditions by the AHA/ACC guidelines. Its use should be encouraged for the diagnosis, management and prognostication of, in particular decompensated cardiac failure, unstable coronary syndromes and aortic stenosis.

The role of BtNP in patients presenting for low risk surgery has not been specifically examined but in asymptomatic patients is probably not indicated.

A good functional capacity with a metabolic equivalent (MET) ≥4 can be equated to a New York Heart Association (NYHA) class I. BtNP levels are strongly associated with NYHA class in patients with clinically stable chronic cardiac failure [117]. Patients classed NYHA I were found to have BNP average (SD) levels of 26.3 (7.2) pg.ml$^{-1}$, below the lowest identified discrimination point of 35 pg.ml$^{-1}$ for BNP [63, 118]. In the short term peri-operative period, patients classified as NYHA grade I experienced no cardiac events [99]. With this in mind, the use of BtNP measurement in patients with good functional capacity (≥ 4 METS) may not be justified.

Clinical risk scores have been inconsistently utilised in the studies reviewed. Where the Goldman index was used BNP identified a group of patients with increased risk across all Goldman classes including class I (odds ratio 3.8, 95% CI 1.9–5.1). The predictive levels of BNP with a cut-off point of 189 pg.ml$^{-1}$ had an area under the curve of 0.84 in comparison to the Goldman index with an area under the curve of 0.61 [99]. Where the revised cardiac risk index (RCRI) has been used it was found that, as expected, higher risk categories have an increasing likelihood of cardiac events, but that an optimally derived BNP threshold of 108.5 pg.ml$^{-1}$ (area under the curve 0.97) was able to identify patients at higher risk of
cardiac events in patients with a RCRI score of 0 and 1 (p = 0.004 and p < 0.001) [101]. When compared to dobutamine stress echocardiography (DSE), with a reported sensitivity and specificity of 85% (95% CI 74%–97%) and 70% (95% CI 62%–79%) respectively for the prediction of 30-day major adverse cardiac events (cardiac death and non-fatal myocardial infarction) in vascular surgical patients, the sensitivity and specificity for BtNP for the same outcome was 83% (95% CI 69%–91%) and 73% (95% CI 68%–77%) [110, 119].

With BtNP constantly performing better than ‘traditional’ clinical risk scores and pre-operative diagnostic tests, I would argue that it should find its place as the next step in the peri-operative cardiovascular evaluation. Faced with a patient undergoing major or intermediate risk surgery, who does not have the ability to function at ≥ 4 METS without symptoms, BtNP offers a very attractive, relatively non-invasive risk stratification tool.

The measurement of BtNP allows quantification of peri-operative risk, which is proportional to the BtNP level. Determining the specific cause of the raised levels entails further cardiac investigations in the form of echocardiography, DSE or angiography [54, 99, 120]. BtNP risk stratification will allow tailored intervention in the form of pre-operative optimisation as well as targeted intra and postoperative management. It may additionally aid in the decision making process around the management of the presenting surgical problem, with more conservative measures being offered to those at significantly higher risk. The term high risk surgery refers to surgery that carries with it a reported cardiac risk of 5% [1]. When considering the study of the largest cohort of patients examined, a BNP level > 300 pg.ml$^{-1}$ had a 40% risk of major adverse cardiac events and an 81% risk of cardiac events (cardiac death, non-fatal myocardial infarction, acute pulmonary oedema and ventricular tachycardia). A level of 200–300 pg.ml$^{-1}$ had a 4.9% risk of major adverse cardiac events and a 13% risk of cardiac events. Only when a level of 100–200 pg.ml$^{-1}$ was reached did the cardiac event rate fail to reach 5% [99]. An analysis of the short term (< 30 days) studies in patients undergoing vascular surgery shows that of the 166 patients with a BtNP level above the discriminatory threshold, 25% (43 patients) would have a major adverse cardiac event [110]. It is probably prudent to suggest that in patients with BtNP levels approaching or consistent with the diagnosis of cardiac failure (BNP > 400 pg.ml$^{-1}$, NT-pro-BNP > 900 pg.ml$^{-1}$), elective surgery should be postponed until the patient’s medical treatment has been fully optimised [57, 69].

A significant rise in postoperative BtNP may identify patients who are unable to cope with the myocardial strain imposed on them and are undergoing a degree of myocardial decompensation [107, 115]. This holds the promise of postoperative secondary risk stratification, similar to the manner in which a postoperative rise in troponins functions as a marker of myocardial injury. Due to normal fluctuations a 70% increase in BNP levels and a 50% increase in NT-pro-BNP levels have been found to constitute a significant change from baseline in patients with stable cardiac failure [24, 121]. As has been shown by Mahla et al., these levels are not applicable in the peri-operative setting with the median in patients with cardiovascular events increasing by 292% (551–1612 pg.ml$^{-1}$) and in those without events by 238% (179–420 pg.ml$^{-1}$) [107]. What seems to be of importance is the actual level reached, rather than the percentage change. Their optimal discriminatory threshold of 860 pg.ml$^{-1}$ is of particular interest as it is very close to the level of 900 pg.ml$^{-1}$, used to identify patients with acute cardiac failure [69]. The implementation of optimal postoperative treatment of these patients could be guided by the serial monitoring of BNP levels [72, 122]. BtNP levels remain to be fully defined in the post-operative period, but it seems intuitive that a level consistent with the diagnosis of cardiac failure in the non operative scenario will result in a poor outcome in the postoperative scenario. Perhaps it is time to consider the use of a postoperative rise in BtNP levels as a marker of a myocardium at risk of failure and aim to develop treatment algorithms similar to those for ACS [123].

Confounding variables in the peri-operative period

Renal failure

Although our understanding of the effects of renal failure on natriuretic peptide metabolism has improved, the effect of impaired renal function on the prognostic ability of BtNP remains to be fully elucidated [124]. The optimal predictive performance of NT-pro-BNP has been shown in patients with a glomerular filtration rate ≥ 90 ml.min$^{-1}$ 1.73 m$^{-2}$ while in patients with a glomerular filtration rate of ≤ 30 ml.min$^{-1}$ 1.73 m$^{-2}$ its prognostic value was completely lost [108]. It is important to remember that patients with progressive renal failure will have cardiovascular dysfunction coupled to their degree of renal failure, which will in itself result in higher levels of BtNP [124].

Body mass index

The impact of BMI on BtNP levels in the peri-operative patient remains largely unexplored and ignored as a possible confounder in many of the studies reported. Obesity is a well recognised risk factor for the development of cardiac failure and an independent predictor of acute myocardial infarction in medical patients, but it
appears that obesity is associated with an improved survival in patients with cardiac failure, which has given rise to the term the obesity paradox [125–127]. In patients with a high BMI, BtNP levels are lower than in patients with a lower BMI [44].

When examining patients with cardiac failure, those with a BMI > 30 kg.m⁻² had lower BNP levels than those with a BMI <20 kg.m⁻² (median 747 pg.ml⁻¹ vs median 332 pg.ml⁻¹, p = 0.0001) [128, 129]. Despite this BMI-related variation in cardiac failure, a NT-pro–BNP cut-off point of 300 pg.ml⁻¹ retained its exclusion utility, as did the age adjusted inclusion cut-off points [68, 130]. In contrast BNP cut-off points required adjustment to ≥54 pg.ml⁻¹ for a BMI ≥ 35 kg.m⁻², and ≥170 pg.ml⁻¹ for those with a BMI < 25 kg.m⁻² [68, 128, 130, 131].

When making use of BtNP for prognostication, NT-pro–BNP once again retained its prognostic ability across different weight categories with a discrimination level of > 986 pg.ml⁻¹ [130]. With BNP the optimal discrimination point for death or urgent transplant had to be adjusted to 342 pg.ml⁻¹ for patients with a BMI ≥ 30 kg.m⁻². Therefore BMI affects the optimal prognostic threshold of BNP and care should be taken to identify and correct for patients with BMIs that fall at the extremes of normal (BMI < 20 kg.m⁻² or ≥ 35 kg.m⁻²).

### Table 5 Proposed peri-operative research agenda for BtNP.

<table>
<thead>
<tr>
<th>Factors related to BtNP</th>
<th>Evidence base</th>
<th>Research recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Which biomarker should be studied?</strong></td>
<td>Both markers yield clinically similar information. NT-pro-BNP may have some advantage over BNP [52, 54, 55, 136, 137].</td>
<td>NT-pro-BNP may have advantages over BNP but either marker may be used [24, 136].</td>
</tr>
<tr>
<td><strong>Age as a confounder</strong></td>
<td>Age adjusted discriminatory thresholds are of significantly more clinical value than a single level [40, 69].</td>
<td>The stratification of patient cohorts according to age groups of &lt; 50, 50–75, and &gt; 75 years is suggested [69].</td>
</tr>
<tr>
<td><strong>Renal failure as a confounder</strong></td>
<td>BtNP levels and prognostic ability are affected by renal failure [37, 108, 124].</td>
<td>Care should be taken to identify and correct for patients with severe renal failure.</td>
</tr>
<tr>
<td><strong>BMI as a confounder</strong></td>
<td>BtNP normal values are significantly altered by BMI. BNP more so than NT-pro–BNP [44, 137].</td>
<td>Care should be taken to identify and correct for patients with BMI &lt; 20 kg.m⁻² or ≥ 35 kg.m⁻² [128, 129].</td>
</tr>
<tr>
<td><strong>Risk determination</strong></td>
<td>Higher levels of BtNP are associated with increased cardiac risk [54, 99].</td>
<td>BtNP risk ranges will be of more clinical value than a single threshold level [99].</td>
</tr>
<tr>
<td><strong>Outcome period</strong></td>
<td>Discriminatory thresholds are affected by the event time horizon (see text).</td>
<td>BtNP ranges should be determined and reported for short (&lt; 30 days), intermediate (&lt; 180 days) and long (&gt; 180 days) term outcomes.</td>
</tr>
<tr>
<td><strong>Pre-operative application of BtNP</strong></td>
<td>Patients with acute dyspnoea, ACS, diagnosed heart failure [61].</td>
<td>BtNP studies should focus on defining its role in risk stratification for patients presenting for major surgery with poor effort tolerance [1].</td>
</tr>
<tr>
<td><strong>Pre-operative BtNP targets</strong></td>
<td>Reductions in BtNP levels are probably effective in reducing morbidity and mortality [70, 72, 73].</td>
<td>The impact of pre-operative optimisation on outcome should be evaluated.</td>
</tr>
<tr>
<td><strong>Pre-operative management of therapy</strong></td>
<td>Patients with BtNP guided therapy receive higher doses of beta-blockers, angiotensin converting enzyme inhibitors and diuretics [72, 73, 139].</td>
<td>Aggressive BtNP targeted therapy should be instituted in patients with cardiac failure.</td>
</tr>
<tr>
<td><strong>Postoperative BtNP targets</strong></td>
<td>A postoperative discrimination threshold for NT-pro–BNP of 860 pg.ml⁻¹ has been identified as significant [107].</td>
<td>BNP &gt; 400 pg.ml⁻¹ or NT-pro–BNP &gt; 900 pg.ml⁻¹ should be considered significant [69, 107].</td>
</tr>
<tr>
<td><strong>Postoperative management of therapy</strong></td>
<td>Aggressive medical management should be instituted [72, 139].</td>
<td>Develop and validate treatment algorithms, which include the use of diuretics, beta blockers, vasodilators and ACEI [72].</td>
</tr>
</tbody>
</table>

BtNP, B-type natriuretic peptide; NT-pro-BNP, N-Terminal pro-B-type natriuretic peptide; BNP, B-type natriuretic peptide; BMI, body mass index; ACS, acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitor.
Research agenda

The use of BtNP holds a significant amount of promise for the peri-operative management of patients, but important aspects remain to be clarified. These are reviewed in Table 5.

Conclusion

The ability to accurately predict cardiovascular morbidity and mortality in patients undergoing anaesthesia remains an elusive goal [132]. Our hope is that accurate identification of patients at risk will prompt targeted interventions to improve patient outcome. While no single test is likely to be able to fully assess the multifactorial aspects that play a role in the pathophysiology of peri-operative morbidity and mortality, BtNP provides us with a key to identify and monitor cardiac failure, a vital component of this process.

A single pre-operative BtNP level, or more ideally a pre and postoperative level, drawn as part of the routine peri-operative workup in patients presenting for major or intermediate risk surgery with a poor effort tolerance, may be a useful integrated monitor of cardiac function. It allows both pre-operative risk stratification equal to or possibly better than current prognostic tools, and the opportunity to monitor postoperative changes in cardiovascular functioning [105, 107, 110]. While it may not yet be the final word in peri-operative cardiac risk assessment, BtNP’s most significant contribution may be in refocusing our attention onto the cardinal role that cardiac failure plays in contributing to peri-operative morbidity and mortality.

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