Anaesthesia
Journal of the Association of Anaesthetists of Great Britain and Ireland

Anaesthesia, 2009, **64**, pages 165–178 doi:10.1111/j.1365-2044.2008.05689.x

REVIEW ARTICLE

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

R. N. Rodseth

Anaesthetic Registrar, Department of Anaesthetics, Nelson R Mandela School of Medicine, Congella, South Africa

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.

Correspondence to: R. N. Rodseth
E-mail: reitzerodseth@gmail.com
Accepted: 22 July 2008

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 peptides (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 clinically 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].

BtNP 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 $ml.min^{-1}$ reduction in creatinine clearance, from 150 $ml.min^{-1}$ to 30 $ml.min^{-1}$, BNP increased by 9%, 22%, 44% and 89% and NT-pro-BNP increased by 9%, 24%, 46% and 95% respectively [34].

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

Patient age	BNP	NT-pro-BNP
Young adults	< 25 $pg.ml^{-1}$ [38]	< 70 $pg.ml^{-1}$ [38]
45–59 years		< 100 $pg.ml^{-1}$ – males
		< 164 $pg.ml^{-1}$ – females [39]
> 60 years	< 98 $pg.ml^{-1}$ [40]	< 172 $pg.ml^{-1}$ – males
		< 225 $pg.ml^{-1}$ – females [39]

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 $pg.ml^{-1}$.

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 cardiomyocytes [44]. As previously discussed, renal failure has a significant impact on natriuretic peptides resulting in higher normal values.

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 a raised BtNP.

In patients presenting to the emergency department with dyspnoea and without cardiac failure, the most common causes for a raised NT-pro-BNP were of pulmonary origin (33%), followed by cardiac related causes (20%). In 20% of patients no diagnosis could be made [64]. Thus in patients with levels that fall into the intermediate zone, the use of traditional clinical features of cardiac failure, together with an appreciation for the differential diagnosis of a raised BtNP will assist the clinician in making an accurate diagnosis.

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

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

BtNP, B-type natriuretic peptides.

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.

Acute heart failure	BNP	NT-pro-BNP
Inclusion	> 400 pg.ml^{-1} [57]	< 50 years – > 450 pg.ml^{-1} 50–75 years – > 900 pg.ml^{-1} > 75 years – > 1800 pg.ml^{-1} [69] Severe chronic renal failure and < 50 years – > 1200 pg.ml^{-1} [124]
Exclusion	< 100 pg.ml^{-1} [58]	< 300 pg.ml^{-1} [69]

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 BtNP 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 BtNP 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 BtNP levels [74, 75]. Following acute myocardial infarction, BtNP levels correlate with left ventricular ejection fraction ($r = -0.63$, $p < 0.0001$) and are higher in patients in whom remodelling occurs (195 $pg.ml^{-1}$ vs 320 $pg.ml^{-1}$; $p = 0.010$) [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 infraction (median 203.5 $pg.ml^{-1}$), unstable angina (77.9 $pg.ml^{-1}$) and patients without acute coronary syndrome (ACS) (27.7 $pg.ml^{-1}$) [78]. Despite BNP being significantly more sensitive in the diagnosis of non-ST segment myocardial infarction than troponin-I (70.8% vs 50.7%, 95% 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 days) and long term (> 30 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 (≤ 98 $pg.ml^{-1}$) and 27.1% in the highest decile (> 4634 $pg.ml^{-1}$) [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 (risk ratio 0.46, 95% CI, 0.21–1.00) and similarly patients with NT-pro-BNP elevations ≥ 237 $pg.ml^{-1}$ were observed to have a lower mortality following revascularization (7.0% 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 a 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 infraction, 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 BtNP 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 BtNP 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 BtNP in non cardiac surgery.

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

BtNP, 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 postoperative 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.

Factors related to BtNP	Evidence base	Research recommendations
Which biomarker should be studied?	Both markers yield clinically similar information. NT-pro-BNP may have some advantage over BNP [52, 54, 55, 136, 137].	NT-pro-BNP may have advantages over BNP but either marker may be used [24, 136].
Age as a confounder	Age adjusted discriminatory thresholds are of significantly more clinical value than a single level [40, 69].	The stratification of patient cohorts according to age groups of < 50, 50–75, and > 75 years is suggested [69].
Renal failure as a confounder	BtNP levels and prognostic ability are affected by renal failure [37, 108, 124].	Care should be taken to identify and to correct for patients with severe renal failure. Patient serum creatinine should be reported on. Further investigation into its effect on the utility of BtNP is warranted [108, 124].
BMI as a confounder	BtNP normal values are significantly altered by BMI. BNP more so than NT-pro-BNP [44, 137].	Care should be taken to identity and correct for patients with BMI < 20$kg.m^{-2}$ or ≥ 35$kg.m^{-2}$ [128, 129].
Risk determination	Higher levels of BtNP are associated with increased cardiac risk [54, 99].	BtNP risk ranges will be of more clinical value than a single threshold level [99].
Outcome period	Discriminatory thresholds are affected by the event time horizon (see text).	BtNP ranges should be determined and reported for short (< 30 days), intermediate (< 180 days) and long (> 180 days) term outcomes.
Pre-operative application of BtNP	Patients with acute dyspnoea, ACS, diagnosed heart failure [61]. Peri-operative investigations have focused on major or intermediate risk surgery [99, 102].	BtNP studies should focus on defining its role in risk stratification for patients presenting for major surgery with poor effort tolerance [1].
Pre-operative BtNP targets	Reductions in BtNP levels are probably effective in reducing morbidity and mortality [70, 72, 73]. Significant mortality increases are seen with levels of BNP > 173 $pg.ml^{-1}$ and NT-pro-BNP levels > 900–1000 $pg.ml^{-1}$ [40, 138]. BNP levels of < 100–250 $pg.ml^{-1}$ as a therapeutic targets have been proposed [72, 73].	The impact of pre-operative optimisation on outcome should be evaluated. BNP < 200–250 $pg.ml^{-1}$ or NT-pro-BNP < 800–900 $pg.ml^{-1}$ where possible should be targeted. Patients with a BNP > 400 $pg.ml^{-1}$ or NT-pro-BNP > 900 $pg.ml^{-1}$ should be postponed until medical treatment is optimised.
Pre-operative management of therapy	Patients with BtNP guided therapy receive higher doses of beta-blockers, angiotensin converting enzyme inhibitors and diuretics [72, 73, 139].	Aggressive BtNP targeted therapy should be instituted in patients with cardiac failure.
Postoperative BtNP targets	A postoperative discrimination threshold for NT-pro-BNP of 860 $pg.ml^{-1}$ has been identified as significant [107].	BNP > 400 $pg.ml^{-1}$ or NT-pro-BNP > 900 $pg.ml^{-1}$ should be considered significant [69, 107].
Postoperative management of therapy	Aggressive medical management should be instituted [72, 139]. Epidural use has shown decrease in levels [122]. Non response or increase in levels is a poor prognostic factor [140, 141].	Develop and validate treatment algorithms, which include the use of diuretics, beta blockers, vasodilators and ACEI [72]. Evaluate the role of epidurals in minimising increases in levels. Identify and intensify management in non responders.

BtNP, B-type natriuretic peptides; 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.

Acknowledgements

Dr Bruce Biccard, Department of Anaesthetics, Nelson R Mandela School of Medicine, is thanked for his invaluable help and support in the preparation of this paper.

References

1 Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *Circulation* 2007; **116**: 1971–96.

2 Falcone RA, Nass C, Jermyn R, et al. The value of preoperative pharmacologic stress testing before vascular surgery using ACC/AHA guidelines: a prospective, randomized trial. *Journal of Cardiothoracic and Vascular Anesthesia* 2003; **17**: 694–8.

3 McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *New England Journal of Medicine* 2004; **351**: 2795–804.

4 Wiesbauer F, Schlager O, Domanovits H, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity: a systematic review and meta-analysis. *Anesthesia and Analgesia* 2007; **104**: 27–41.

5 Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990; **72**: 153–84.

6 Hammill BG, Curtis LH, Bennett-Guerrero E, et al. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 2008; **108**: 559–67.

7 Hernandez AF, Whellan DJ, Stroud S, Sun JL, O'Connor CM, Jollis JG. Outcomes in heart failure patients after major noncardiac surgery. *Journal of the American College of Cardiology* 2004; **44**: 1446–53.

8 Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *New England Journal of Medicine* 1977; **297**: 845–50.

9 Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999; **100**: 1043–9.

10 Eagle KA, Brundage BH, Chaitman BR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Journal of the American College of Cardiology* 1996; **27**: 910–48.

11 Fonseca C, Morais H, Mota T, et al. The diagnosis of heart failure in primary care: value of symptoms and signs. *European Journal of Heart Failure* 2004; **6**: 795–800, 21-2.

12 Azevedo A, Bettencourt P, Pimenta J, et al. Clinical syndrome suggestive of heart failure is frequently attributable to non-cardiac disorders – population-based study. *European Journal of Heart Failure* 2007; **9**: 391–6.

13 McCullough PA. B-type natriuretic peptides. A diagnostic breakthrough in heart failure. *Minerva Cardioangiologica* 2003; **51**: 121–9.

14 de Denus S, Pharand C, Williamson DR. Brain natriuretic peptide in the management of heart failure: the versatile neurohormone. *Chest* 2004; **125**: 652–68.

15 Nakao K, Ogawa Y, Suga S, Imura H. Molecular biology and biochemistry of the natriuretic peptide system. I: Natriuretic peptides. *Journal of Hypertension* 1992; **10**: 907–12.

16 Gardner DG, Chen S, Glenn DJ, Grigsby CL. Molecular biology of the natriuretic peptide system: implications for

physiology and hypertension. *Hypertension* 2007; **49**: 419–26.
17 Nishikimi T, Maeda N, Matsuoka H. The role of natriuretic peptides in cardioprotection. *Cardiovascular Research* 2006; **69**: 318–28.
18 Hystad ME, Geiran OR, Attramadal H, et al. Regional cardiac expression and concentration of natriuretic peptides in patients with severe chronic heart failure. *Acta Physiologica Scandinavica* 2001; **171**: 395–403.
19 Tsuruda T, Boerrigter G, Huntley BK, et al. Brain natriuretic peptide is produced in cardiac fibroblasts and induces matrix metalloproteinases. *Circulation Research* 2002; **91**: 1127–34.
20 Goetze JP, Gore A, Moller CH, Steinbruchel DA, Rehfeld JF, Nielsen LB. Acute myocardial hypoxia increases BNP gene expression. *The FASEB Journal* 2004; **18**: 1928–30.
21 Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *European Journal of Heart Failure* 2004; **6**: 257–60.
22 Durocher D, Grepin C, Nemer M. Regulation of gene expression in the endocrine heart. *Recent Progress in Hormone Research* 1998; **53**: 7–23; discussion 2–3.
23 Maack T, Suzuki M, Almeida FA, et al. Physiological role of silent receptors of atrial natriuretic factor. *Science* 1987; **238**: 675–8.
24 Wu AH, Smith A, Wieczorek S, et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. *The American Journal of Cardiology* 2003; **92**: 628–31.
25 Luchner A, Stevens TL, Borgeson DD, et al. Differential atrial and ventricular expression of myocardial BNP during evolution of heart failure. *American Journal of Physiology* 1998; **274**: H1684–9.
26 Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *New England Journal of Medicine* 1998; **339**: 321–8.
27 Koller KJ, Goeddel DV. Molecular biology of the natriuretic peptides and their receptors. *Circulation* 1992; **86**: 1081–8.
28 Lewis J, Salem MM, Chertow GM, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. *American Journal of Kidney Diseases* 2000; **36**: 767–74.
29 Allgren RL, Marbury TC, Rahman SN, et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *New England Journal of Medicine* 1997; **336**: 828–34.
30 Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005; **293**: 1900–5.
31 Munger MA, Ng TM, Van Tassell BW. Controversy and conflict in the treatment of acute decompensated heart failure: nesiritide as evidence-based treatment. *Pharmacotherapy* 2007; **27**: 619–25.
32 McDowell G, Coutie W, Shaw C, Buchanan KD, Struthers AD, Nicholls DP. The effect of the neutral endopeptidase inhibitor drug, candoxatril, on circulating levels of two of the most potent vasoactive peptides. *British Journal of Clinical Pharmacology* 1997; **43**: 329–32.
33 Barber MN, Kanagasundaram M, Anderson CR, Burrell LM, Woods RL. Vascular neutral endopeptidase inhibition improves endothelial function and reduces intimal hyperplasia. *Cardiovascular Research* 2006; **71**: 179–88.
34 Richards M, Nicholls MG, Espiner EA, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *Journal of the American College of Cardiology* 2006; **47**: 52–60.
35 McCullough PA, Sandberg KR. Sorting out the evidence on natriuretic peptides. *Reviews in Cardiovascular Medicine* 2003; **4** (Suppl. 4): S13–9.
36 Ng LL, Loke IW, Davies JE, et al. Community screening for left ventricular systolic dysfunction using plasma and urinary natriuretic peptides. *Journal of the American College of Cardiology* 2005; **45**: 1043–50.
37 Austin WJ, Bhalla V, Hernandez-Arce I, et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *American Journal of Clinical Pathology* 2006; **126**: 506–12.
38 Daniels LB, Allison MA, Clopton P, et al. Use of natriuretic peptides in pre-participation screening of college athletes. *International Journal of Cardiology* 2008; **124**: 411–14.
39 Galasko GI, Lahiri A, Barnes SC, Collinson P, Senior R. What is the normal range for N-terminal pro-brain natriuretic peptide? How well does this normal range screen for cardiovascular disease? *European Heart Journal* 2005; **26**: 2269–76.
40 Alehagen U, Goetze JP, Dahlstrom U. Reference intervals and decision limits for B-type natriuretic peptide (BNP) and its precursor (Nt-proBNP) in the elderly. *Clinica Chimica Acta* 2007; **382**: 8–14.
41 Chang AY, Abdullah SM, Jain T, et al. Associations among androgens, estrogens, and natriuretic peptides in young women: observations from the Dallas Heart Study. *Journal of the American College of Cardiology* 2007; **49**: 109–16.
42 Sarzani R, Dessi-Fulgheri P, Paci VM, Espinosa E, Rappelli A. Expression of natriuretic peptide receptors in human adipose and other tissues. *Journal of Endocrinological Investigation* 1996; **19**: 581–5.
43 Dessi-Fulgheri P, Sarzani R, Tamburrini P, et al. Plasma atrial natriuretic peptide and natriuretic peptide receptor gene expression in adipose tissue of normotensive and hypertensive obese patients. *Journal of Hypertension* 1997; **15**: 1695–9.
44 Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation* 2005; **112**: 2163–8.
45 Nishikimi T, Yoshihara F, Morimoto A, et al. Relationship between left ventricular geometry and natriuretic peptide levels in essential hypertension. *Hypertension* 1996; **28**: 22–30.

46 Karagiannis A, Tziomalos K, Zamboulis C. Plasma B-type natriuretic peptide is related to left ventricular mass in hypertensive patients. *European Heart Journal* 2004; **25**: 1967.
47 Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Biochemical diagnosis of impaired left ventricular ejection fraction – comparison of the diagnostic accuracy of brain natriuretic peptide (BNP) and amino terminal proBNP (NT-proBNP). *Clinical Chemistry and Laboratory Medicine* 2004; **42**: 159–63.
48 Tsutamoto T, Sakai H, Nishiyama K, et al. Direct comparison of transcardiac increase in brain natriuretic peptide (BNP) and N-terminal proBNP and prognosis in patients with chronic heart failure. *Circulation Journal* 2007; **71**: 1873–8.
49 Chien TI, Chen HH, Kao JT. Comparison of Abbott AxSYM and Roche Elecsys 2010 for measurement of BNP and NT-proBNP. *Clinica Chimica Acta* 2006; **369**: 95–9.
50 Hammerer-Lercher A, Puschendorf B, Mair J. Cardiac natriuretic peptides: new laboratory parameters in heart failure patients. *Clinical Laboratory* 2001; **47**: 265–77.
51 Holmes SJ, Espiner EA, Richards AM, Yandle TG, Frampton C. Renal, endocrine, and hemodynamic effects of human brain natriuretic peptide in normal man. *The Journal of Clinical Endocrinology and Metabolism* 1993; **76**: 91–6.
52 Mair J, Falkensammer G, Poelzl G, Hammerer-Lercher A, Griesmacher A, Pachinger O. B-type natriuretic peptide (BNP) is more sensitive to rapid hemodynamic changes in acute heart failure than N-terminal proBNP. *Clinica Chimica Acta* 2007; **379**: 163–6.
53 Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *Journal of the American College of Cardiology* 2006; **47**: 345–53.
54 Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clinical Chemistry* 2006; **52**: 1528–38.
55 Sakai H, Tsutamoto T, Ishikawa C, et al. Direct comparison of brain natriuretic peptide (BNP) and N-terminal pro-BNP secretion and extent of coronary artery stenosis in patients with stable coronary artery disease. *Circulation Journal* 2007; **71**: 499–505.
56 Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. *Circulation* 2007; **115**: 3103–10.
57 Korenstein D, Wisnivesky JP, Wyer P, Adler R, Ponieman D, McGinn T. The utility of B-type natriuretic peptide in the diagnosis of heart failure in the emergency department: a systematic review. *BMC Emergency Medicine* 2007; **7**: 6.
58 Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *New England Journal of Medicine* 2002; **347**: 161–7.
59 Maisel A. B-type natriuretic peptide measurements in diagnosing congestive heart failure in the dyspneic emergency department patient. *Reviews in Cardiovascular Medicine* 2002; **3** (Suppl. 4): S10–7.
60 Gibler WB, Blomkalns AL, Collins SP. Evaluation of chest pain and heart failure in the emergency department: impact of multimarker strategies and B-type natriuretic peptide. *Reviews in Cardiovascular Medicine* 2003; **4** (Suppl. 4): S47–55.
61 Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *The American Journal of Cardiology* 2005; **95**: 948–54.
62 Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *New England Journal of Medicine* 2004; **350**: 655–63.
63 Cuthbertson BH, Amiri AR, Croal BL, Rajagopalan S, Brittenden J, Hillis GS. Utility of B-type natriuretic peptide in predicting medium-term mortality in patients undergoing major non-cardiac surgery. *The American Journal of Cardiology* 2007; **100**: 1310–3.
64 van Kimmenade RR, Pinto YM, Bayes-Genis A, Lainchbury JG, Richards AM, Januzzi JL Jr. Usefulness of intermediate amino-terminal pro-brain natriuretic peptide concentrations for diagnosis and prognosis of acute heart failure. *The American Journal of Cardiology* 2006; **98**: 386–90.
65 Arbab-Zadeh A, Dijk E, Prasad A, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation* 2004; **110**: 1799–805.
66 McCullough PA, Duc P, Omland T, et al. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. *American Journal of Kidney Diseases* 2003; **41**: 571–9.
67 Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *Journal of the American College of Cardiology* 2002; **40**: 976–82.
68 Januzzi JL, van Kimmenade R, Lainchbury J, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *European Heart Journal* 2006; **27**: 330–7.
69 Januzzi JL Jr, Chen-Tournoux AA, Moe G. Amino-terminal pro-B-type natriuretic peptide testing for the diagnosis or exclusion of heart failure in patients with acute symptoms. *The American Journal of Cardiology* 2008; **101**: 29–38.
70 Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005; **330**: 625.
71 Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure

guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; **355**: 1126–30.
72 Jourdain P, Jondeau G, Funck F, et al. Plasma brain natriuretic peptide-guided therapy to improve outcome in heart failure: the STARS-BNP Multicenter Study. *Journal of the American College of Cardiology* 2007; **49**: 1733–9.
73 Valle R, Aspromonte N, Giovinazzo P, et al. B-type natriuretic Peptide-guided treatment for predicting outcome in patients hospitalized in sub-intensive care unit with acute heart failure. *Journal of Cardiac Failure* 2008; **14**: 219–24.
74 Cochet A, Zeller M, Cottin Y, et al. The extent of myocardial damage assessed by contrast-enhanced MRI is a major determinant of N-BNP concentration after myocardial infarction. *European Journal of Heart Failure* 2004; **6**: 555–60.
75 Ceriani L, Giovanella L. Cardiac natriuretic peptides after myocardial infarction: relationship with infarct size, left ventricular function and remodelling assessed by 99mTc-sestamibi gated-single photon emission tomography. *Clinical Chemistry and Laboratory Medicine* 2007; **45**: 226–31.
76 Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin: new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation* 1998; **97**: 1921–9.
77 Cerisano G, Pucci PD, Sulla A, et al. Relation between plasma brain natriuretic peptide, serum indexes of collagen type I turnover, and left ventricular remodeling after reperfused acute myocardial infarction. *The American Journal of Cardiology* 2007; **99**: 651–6.
78 Bassan R, Potsch A, Maisel A, et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. *European Heart Journal* 2005; **26**: 234–40.
79 Brown A, George J, Murphy MJ, Struthers A. Could BNP screening of acute chest pain cases lead to safe earlier discharge of patients with non-cardiac causes? A pilot study. *QJM* 2007; **100**: 755–61.
80 Heeschen C, Hamm CW, Mitrovic V, Lantelme NH, White HD. N-terminal pro-B-type natriuretic peptide levels for dynamic risk stratification of patients with acute coronary syndromes. *Circulation* 2004; **110**: 3206–12.
81 Jernberg T, Stridsberg M, Venge P, Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *Journal of the American College of Cardiology* 2002; **40**: 437–45.
82 Omland T, Persson A, Ng L, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002; **106**: 2913–8.
83 James SK, Lindback J, Tilly J, et al. Troponin-T and N-terminal pro-B-type natriuretic peptide predict mortality benefit from coronary revascularization in acute coronary syndromes: a GUSTO-IV substudy. *Journal of the American College of Cardiology* 2006; **48**: 1146–54.
84 Steen H, Futterer S, Merten C, Junger C, Katus HA, Giannitsis E. Relative role of NT-pro BNP and cardiac troponin T at 96 hours for estimation of infarct size and left ventricular function after acute myocardial infarction. *Journal of Cardiovascular Magnetic Resonance* 2007; **9**: 749–58.
85 Jernberg T, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide in relation to inflammation, myocardial necrosis, and the effect of an invasive strategy in unstable coronary artery disease. *Journal of the American College of Cardiology* 2003; **42**: 1909–16.
86 Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *New England Journal of Medicine* 2005; **352**: 666–75.
87 Schnabel R, Lubos E, Rupprecht HJ, et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina: results from the AtheroGene study. *Journal of the American College of Cardiology* 2006; **47**: 552–8.
88 McDonagh TA, Robb SD, Murdoch DR, et al. Biochemical detection of left-ventricular systolic dysfunction. *Lancet* 1998; **351**: 9–13.
89 Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide to detect preclinical ventricular systolic or diastolic dysfunction: a community-based study. *Circulation* 2004; **109**: 3176–81.
90 Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. *Heart* 2002; **87**: 131–5.
91 Fuat A, Murphy JJ, Hungin AP, et al. The diagnostic accuracy and utility of a B-type natriuretic peptide test in a community population of patients with suspected heart failure. *The British Journal of General Practice* 2006; **56**: 327–33.
92 Rao A, Hodgson L, Pearce D, Walsh J. BNP in the community – still work to be done. *International Journal of Cardiology* 2008; **124**: 228–30.
93 Illango RK. Utilizing NT-proBNP in the selection of risks for life insurance. *Journal of Insurance Medicine* 2007; **39**: 182–91.
94 Roch A. What does high NT-proBNP mean in septic shock patients? A part of the puzzle. *Critical Care* 2007; **11**: 122.
95 Mokart D, Sannini A, Brun JP, et al. N-terminal pro-brain natriuretic peptide as an early prognostic factor in cancer patients developing septic shock. *Critical Care* 2007; **11**: R37.
96 Phua J, Lim TK, Lee KH. B-type natriuretic peptide: issues for the intensivist and pulmonologist. *Critical Care Medicine* 2005; **33**: 2094–13.
97 Omland T. Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. *Critical Care Medicine* 2008; **36**: S17–27.

98 Longhitano S, Coriat P, Agro F. Postoperative myocardial infarction: pathophysiology, new diagnostic criteria, prevention. *Minerva Anestesiologica* 2006; **72**: 965–83.
99 Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. *Heart* 2006; **92**: 1645–50.
100 Yeh HM, Lau HP, Lin JM, Sun WZ, Wang MJ, Lai LP. Preoperative plasma N-terminal pro-brain natriuretic peptide as a marker of cardiac risk in patients undergoing elective non-cardiac surgery. *The British Journal of Surgery* 2005; **92**: 1041–5.
101 Gibson SC, Payne CJ, Byrne DS, Berry C, Dargie HJ, Kingsmore DB. B-type natriuretic peptide predicts cardiac morbidity and mortality after major surgery. *The British Journal of Surgery* 2007; **94**: 903–9.
102 Cuthbertson BH, Amiri AR, Croal BL, et al. Utility of B-type natriuretic peptide in predicting perioperative cardiac events in patients undergoing major non-cardiac surgery. *British Journal of Anaesthesia* 2007; **99**: 170–6.
103 Cuthbertson BH, Card G, Croal BL, McNeilly J, Hillis GS. The utility of B-type natriuretic peptide in predicting postoperative cardiac events and mortality in patients undergoing major emergency non-cardiac surgery. *Anaesthesia* 2007; **62**: 875–81.
104 Berry C, Kingsmore D, Gibson S, et al. Predictive value of plasma brain natriuretic peptide for cardiac outcome after vascular surgery. *Heart* 2006; **92**: 401–2.
105 Feringa HH, Bax JJ, Elhendy A, et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. *The American Journal of Cardiology* 2006; **98**: 111–5.
106 Feringa HH, Schouten O, Dunkelgrun M, et al. Plasma N-terminal pro-B-type natriuretic peptide as long-term prognostic marker after major vascular surgery. *Heart* 2007; **93**: 226–31.
107 Mahla E, Baumann A, Rehak P, et al. N-terminal pro-brain natriuretic peptide identifies patients at high risk for adverse cardiac outcome after vascular surgery. *Anesthesiology* 2007; **106**: 1088–95.
108 Goei D, Schouten O, Boersma E, et al. Influence of renal function on the usefulness of N-terminal pro-B-type natriuretic peptide as a prognostic cardiac risk marker in patients undergoing noncardiac vascular surgery. *The American Journal of Cardiology* 2008; **101**: 122–6.
109 Leibowitz D, Planer D, Rott D, Elitzur Y, Chajek-Shaul T, Weiss AT. Brain Natriuretic Peptide Levels Predict Perioperative Events in Cardiac Patients Undergoing Noncardiac Surgery: A Prospective Study. *Cardiology* 2007; **110**: 266–70.
110 Rodseth RN, Padayachee L, Biccard BM. A meta-analysis of the utility of pre-operative brain natriuretic peptide in predicting early and intermediate-term mortality and major adverse cardiac events in vascular surgical patients. *Anaesthesia* 2008; **63**: 1226–1233.
111 Watanabe M, Murakami M, Furukawa H, Nakahara H. Is measurement of plasma brain natriuretic peptide levels a useful test to detect for surgical timing of valve disease? *International Journal of Cardiology* 2004; **96**: 21–4.
112 Bergler-Klein J, Klaar U, Heger M, et al. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation* 2004; **109**: 2302–8.
113 Eliasdottir SB, Klemenzson G, Torfason B, Valsson F. Brain natriuretic peptide is a good predictor for outcome in cardiac surgery. *Acta Anaesthesiologica Scandinavica* 2008; **52**: 182–7.
114 Hutfless R, Kazanegra R, Madani M, et al. Utility of B-type natriuretic peptide in predicting postoperative complications and outcomes in patients undergoing heart surgery. *Journal of the American College of Cardiology* 2004; **43**: 1873–9.
115 Jeong DS, Kim KH, Kim CY, Kim JS. Relationship between plasma B-type natriuretic peptide and ventricular function in adult cardiac surgery patients. *The Journal of International Medical Research* 2008; **36**: 31–9.
116 Wazni OM, Martin DO, Marrouche NF, et al. Plasma B-type natriuretic peptide levels predict postoperative atrial fibrillation in patients undergoing cardiac surgery. *Circulation* 2004; **110**: 124–7.
117 Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation* 1997; **96**: 509–16.
118 Jourdain P, Funck F, Bellorini M, et al. Bedside B-type natriuretic peptide and functional capacity in chronic heart failure. *European Journal of Heart Failure* 2003; **5**: 155–60.
119 Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart* 2003; **89**: 1327–34.
120 Messer PB, Singh R, McAuley FT, Handley G, Peaston B, Snowden CP. The use of N-terminal pro-B type natriuretic peptide in a pre-operative setting to predict left ventricular systolic dysfunction on echocardiogram. *Anaesthesia* 2008; **63**: 482–7.
121 O'Hanlon R, O'Shea P, Ledwidge M, et al. The biologic variability of B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide in stable heart failure patients. *Journal of Cardiac Failure* 2007; **13**: 50–5.
122 Suttner S, Lang K, Piper SN, Schultz H, Rohm KD, Boldt J. Continuous intra- and postoperative thoracic epidural analgesia attenuates brain natriuretic peptide release after major abdominal surgery. *Anesthesia and Analgesia* 2005; **101**: 896–903.
123 Adesanya AO, de Lemos JA, Greilich NB, Whitten CW. Management of perioperative myocardial infarction in noncardiac surgical patients. *Chest* 2006; **130**: 584–96.
124 DeFilippi C, van Kimmenade RR, Pinto YM. Amino-terminal pro-B-type natriuretic peptide testing in renal disease. *The American Journal of Cardiology* 2008; **101**: 82–8.

125 Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**: 937–52.
126 Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *Journal of the American College of Cardiology* 2001; **38**: 789–95.
127 Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *The American Journal of Cardiology* 2003; **91**: 891–4.
128 Horwich TB, Hamilton MA, Fonarow GC. B-type natriuretic peptide levels in obese patients with advanced heart failure. *Journal of the American College of Cardiology* 2006; **47**: 85–90.
129 Krauser DG, Lloyd-Jones DM, Chae CU, et al. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy. *American Heart Journal* 2005; **149**: 744–50.
130 Bayes-Genis A, Lloyd-Jones DM, van Kimmenade RR, et al. Effect of body mass index on diagnostic and prognostic usefulness of amino-terminal pro-brain natriuretic peptide in patients with acute dyspnea. *Archives of Internal Medicine* 2007; **167**: 400–7.
131 Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure. Results from the Breathing Not Properly Multinational Study. *American Heart Journal* 2006; **151**: 999–1005.
132 Ridley S. Cardiac scoring systems – what is their value? *Anaesthesia* 2003; **58**: 985–91.
133 Knudsen CW, Clopton P, Westheim A, et al. Predictors of elevated B-type natriuretic peptide concentrations in dyspneic patients without heart failure: an analysis from the breathing not properly multinational study. *Annals of Emergency Medicine* 2005; **45**: 573–80.
134 van Kimmenade RR, Pinto YM, Januzzi JL Jr. Importance and interpretation of intermediate (gray zone) amino-terminal pro-B-type natriuretic peptide concentrations. *The American Journal of Cardiology* 2008; **101**: 39–42.
135 Baggish AL, van Kimmenade RR, Januzzi JL Jr. The differential diagnosis of an elevated amino-terminal pro-B-type natriuretic peptide level. *The American Journal of Cardiology* 2008; **101**: 43–8.
136 Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; **112**: e154–235.
137 Bayes-Genis A, DeFilippi C, Januzzi JL Jr. Understanding amino-terminal pro-B-type natriuretic peptide in obesity. *The American Journal of Cardiology* 2008; **101**: 89–94.
138 Masson S, Latini R. Amino-terminal pro-B-type natriuretic peptides and prognosis in chronic heart failure. *The American Journal of Cardiology* 2008; **101**: 56–60.
139 Murdoch DR, McDonagh TA, Byrne J, et al. Titration of vasodilator therapy in chronic heart failure according to plasma brain natriuretic peptide concentration: randomized comparison of the hemodynamic and neuroendocrine effects of tailored versus empirical therapy. *American Heart Journal* 1999; **138**: 1126–32.
140 Cheng V, Kazanagra R, Garcia A, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *Journal of the American College of Cardiology* 2001; **37**: 386–91.
141 Richards M, Troughton RW. NT-proBNP in heart failure: therapy decisions and monitoring. *European Journal of Heart Failure* 2004; **6**: 351–4.