Utility of B-type natriuretic peptide in predicting perioperative cardiac events in patients undergoing major non-cardiac surgery†

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Background. B-type natriuretic peptide (BNP) levels predict cardiovascular risk in several settings. We hypothesized that they would identify individuals at increased risk of early cardiac complications after major non-cardiac surgery. The current study tests this hypothesis.

Methods. Two hundred and four patients undergoing major non-cardiac surgery were studied. The primary end-point was the development of acute myocardial injury [defined as cardiac troponin I (cTnI) level $>0.32$ ng ml$^{-1}$] or death in the 3 days after surgery.

Results. Preoperative BNP levels were raised in patients who died or suffered perioperative myocardial injury (median 52.2 vs 22.2 pg ml$^{-1}$, $P=0.01$) and BNP predicted this outcome with an area under the receiver operating characteristic curve of 0.72 [95% confidence interval (CI) 0.59–0.86, $P=0.01$]. A preoperative BNP value $>40$ pg ml$^{-1}$ was associated with an increased risk of death or perioperative myocardial injury [odds ratio (OR) 6.8, 95% CI 1.8–25.9, $P=0.003$], and remained independently predictive after correction for the Revised Cardiac Risk Index. Preoperative BNP levels were higher in patients who exhibited new onset atrial fibrillation or ST/T-wave changes on their postoperative ECG (median 50.5 vs 22.5 pg litre$^{-1}$, $P=0.01$). They were also higher in patients who had either elevation of cTnI $>0.32$ ng ml$^{-1}$ or postoperative ECG abnormalities (median 50.4 vs 21.5 pg ml$^{-1}$, $P<0.001$).

Conclusions. In the setting of major non-cardiac surgery, preoperative BNP levels are higher in patients who experience perioperative death and myocardial injury. Larger studies are required to confirm these data and to clarify what BNP levels may add to existing methods of risk stratification.

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Major non-cardiac surgery is associated with significant perioperative mortality and morbidity. The majority of deaths in this setting are related to cardiac complications such as myocardial infarction.1–4 Major surgery is also associated with stroke, non-fatal myocardial ischaemia and infarction, and malignant arrhythmia.1–4 A variety of scoring systems and imaging strategies have been developed to predict such adverse cardiovascular events.1–7 Low predictive accuracy, variations in the risk factors used to calculate the risk score and their weighting, and poor clinical utility have limited the use of risk indices in current clinical practice.

B-type natriuretic peptide (BNP) is a 32 amino acid peptide secreted chiefly from the cardiac ventricles in response to wall stress. It promotes natriuresis, diuresis, and vasodilatation. The blood level of BNP is raised in patients with cardiac disease, particularly those with heart failure.8 It is an important indicator of prognosis both in heart failure8 and after acute myocardial infarction where elevated levels identify patients at high risk of progressive ventricular dilatation, heart failure, or death.8–10 BNP also gives useful information on the presence of diastolic dysfunction,11 and is helpful in the differential diagnosis of
acute breathlessness. In addition, it is released in response to myocardial ischaemia, presumably as a result of increases in wall stress.

The ability of BNP to integrate the effects of several differing facets of myocardial dysfunction makes it useful as an indicator of cardiovascular prognosis in many settings. Early data suggest that it may be of value in the perioperative period. BNP has been used to predict postoperative length of stay and 1 yr mortality in patients undergoing coronary artery bypass surgery, and larger studies are underway in cardiac surgery patients. Likewise, initial reports suggest that levels of BNP and its N-terminal pro-peptide (NT-proBNP) may be of value in predicting cardiovascular complications among patients undergoing non-cardiac surgery. The findings in these initial retrospective small studies require confirmation in larger prospective cohorts using objective end-points. The aim of the current study was to assess whether elevated preoperative BNP levels are associated with an increased risk of death or acute myocardial injury in the first 3 days after major non-cardiac surgery.

Methods

The study protocol was approved by the local research ethics committee, and written informed consent was obtained from all patients. The study was a prospective single centre observational cohort study of consecutive patients undergoing scheduled major non-cardiac surgery. This was defined as major vascular surgery (open aortic surgery, infra-inguinal bypass surgery, axillo-femoral bypass), major gastrointestinal surgery (laparotomy, thoraco-laparotomy), major gynaecological cancer surgery (abdominal hysterectomy and oophorectomy for cancer), and major open urological surgery (cystectomy, radical nephrectomy, total prostatectomy). Patients requiring emergency surgery (surgery required within 24 h) or those undergoing minor or intermediate grade surgery were excluded. Patients were assessed before surgery by an experienced anaesthetist and were considered to be fit for major elective surgery, and not to have clinical evidence of significant fluid and electrolyte imbalance or cardiac failure.

Data collection

Preoperative data collection included the recording of a 12-lead ECG, patient characteristics, medical and surgical history, preoperative medications, and renal and hepatic function. Preoperative blood samples were also obtained for cardiac troponin I (cTnI) and plasma BNP levels. The Revised Cardiac Risk Index was calculated. All surgery was performed under general anaesthesia, and all patients received standard perioperative care. Postoperative data collection included the recording of a 12-lead ECG and blood samples for cTnI levels at 24 and 72 h after surgery. Data were also collected on postoperative mortality and hospital length of stay.

Study end-points

All patients were followed-up by an investigator who was unaware of the patients’ biochemistry results and findings on ECG. The primary end-point was the predictive power of BNP for death or myocardial injury within 72 h of surgery. We have used the terminology myocardial ‘injury’ instead of ‘infarction’ as the latter is difficult to define in this setting because patients often do not have the classical symptoms or ECG changes of myocardial infarction. Reliance on biochemical evidence of damage alone has the advantage of being entirely objective. Acute perioperative myocardial injury was defined as evidence of myocardial cell necrosis (cTnI >0.32 ng ml⁻¹), without preoperative cTnI elevation. This cut-off is the level that exceeds the 99th percentile for a normal population at which the coefficient of variation for the assay being used (Bayer ADVIA Centaur™) decreases below 10%. This is, therefore, the level at which an acute myocardial infarction can be diagnosed using this assay, according to the European Society of Cardiology/American College of Cardiology guidelines.

The secondary composite end-point was the occurrence of either death or postoperative myocardial injury (defined as above) or ECG evidence of acute myocardial ischaemia or arrhythmia (within 72 h of surgery). ECG evidence of ischaemia was defined as the development of new, postoperative, T-wave inversion ≥2 mm, and ST segment deviation ≥2 mm in at least two contiguous chest leads or 1 mm in at least two contiguous limb leads. Arrhythmia was defined as a new, sustained, abnormal cardiac rhythm. All ECGs were analysed by a consultant cardiologist blinded to all other data, including the patients’ clinical status and their biochemistry results. Clinicians responsible for the patients’ care were blinded to the ECG and cTnI results that were obtained for research purposes. They were blinded to BNP results at all times.

Assays

Blood was collected in EDTA and lithium heparin Vacutainer™ tubes, which were immediately centrifuged and the plasma stored at −80°C for later analysis. Plasma BNP was determined before operation, and serum cTnI levels were determined before operation and at 24 and 72 h after operation. Before the preoperative blood sample, patients were asked to lie quietly in the supine position for 30 min in order to eliminate any possible confounding effects of posture and exercise on plasma BNP levels. BNP and cTnI assays were measured using the Bayer ADVIA Centaur™ immunoassay. The lower limit of detection for BNP was 5 pg ml⁻¹, and the coefficients of variation at 48 and 461 pg ml⁻¹ were 3.4% and 2.9%, respectively. The lower limit of detection for cTnI was 0.1 ng ml⁻¹, with a coefficient of variation of 22% at 0.1 ng ml⁻¹ and of 10% at 0.32 ng ml⁻¹.
Power calculation

Prior studies suggest that elevated cTn levels occur in approximately 8–17% of patients undergoing major non-cardiac surgery,18–20 with major cardiovascular complications reported in >30% of high-risk patients.3 Our own pilot data, on 40 patients, suggested the incidence of peri-operative death or objective evidence of myocardial injury (cTnI >0.32 ng ml⁻¹) was 15% (six patients), with a mean preoperative BNP level of 86.5 pg ml⁻¹ in those who had a perioperative cardiac event and 31.5 pg ml⁻¹ in those who did not, with a SD of 20 pg ml⁻¹. We calculated, therefore, that a sample size of 198 patients completing the study would allow us to detect a 30 pg ml⁻¹ difference in BNP levels between patients who did and did not experience the primary end-point, with 90% power at a 5% level of significance.

Statistical analysis

Categorical data are presented as absolute values and percentages. Normally distributed continuous variables are presented as mean and SD. BNP levels exhibited a skewed distribution and are expressed as median and inter-quartile range (IQR). Fisher’s exact t-test was used to test differences between independent categorical data. Differences between two independent groups of continuous data were tested using the t-test or Mann–Whitney U-test as appropriate. Quartiles of BNP were compared using the χ² test for trend (for categorical data) and the Jonckheere–Terpstra test (for ordered continuous data). To test the strength of the association between BNP levels and other continuous variables, Spearman’s rank correlation was used. To establish a BNP cut-off value with appropriate sensitivity and specificity, receiver operating characteristic (ROC) curves were plotted and the area under the curve estimated. Binary logistic regression was used to test the predictive value of BNP levels and other selected parameters. Factors with a P-value of <0.25 in univariable analyses (age and prior use of cardiac medication) were entered into a backward conditional model. A further model included only elevated BNP levels and the Revised Cardiac Risk Index. A P-value of <0.05 was considered significant.

Results

Patient population

From September 2004 to April 2005, 239 patients eligible to take part in the study were approached to participate. Twenty (8%) refused consent. It was not possible to obtain preoperative blood samples from 5 patients (2%), and 10 (4%) patients did not undergo major surgery and were excluded. Of these latter 10 excluded patients, one died before operation and the remaining nine underwent laparoscopic surgery. The remaining 204 patients agreed to take part in the study, were recruited, and completed the trial protocol. Baseline characteristics for this cohort are shown in Table 1. The type of surgery performed and the prevalence of perioperative myocardial injury or death are shown in Table 2. No patients had elevated cTnI levels before operation.

BNP levels and outcome

Twelve patients (6%) experienced acute myocardial injury within 72 h of surgery, and one of these patients died within 3 days of surgery. No other patients in the study cohort died within 30 days of surgery. The relationship between preoperative BNP levels and perioperative death or myocardial injury is shown in Table 1. Preoperative BNP levels were correlated with age and serum creatinine (r=0.56 and 0.26, respectively, both P<0.001). The relationship between BNP quartiles, baseline characteristics, and outcome of the study cohort is shown in Table 3. The area under the ROC curve assessing the utility of BNP in predicting perioperative death or myocardial injury was 0.72 [95% confidence interval (CI) 0.59–0.86, P=0.01] (Fig. 1). A preoperative BNP value of 40 pg ml⁻¹ achieved a sensitivity of 75% and specificity of 70% for detecting perioperative death or myocardial injury. The area under the ROC curve for the Revised Cardiac Risk Index was 0.54 (95% CI 0.38–0.71, P=0.63) (Fig. 1).

Using logistic regression, the only univariable predictor of perioperative death or acute myocardial injury was a preoperative BNP >40 pg ml⁻¹ (Table 4). This remained unchanged in a regression model including BNP >40 pg ml⁻¹, age, and preoperative use of cardiac medication [odds ratio (OR) 6.8, 95% CI 1.8–25.9, P=0.005]. In a further model that included only BNP >40 pg ml⁻¹ and the Revised Cardiac Risk Index, the former remained a strong independent predictor of outcome (OR 7.5, 95% CI 1.9–29.4, P=0.004).

New ECG changes were identified in 14 patients (10 T-wave or ST-segment abnormalities and four with new onset postoperative atrial fibrillation), only one of whom developed cTnI elevation (Table 1). However, preoperative BNP levels were higher in patients who exhibited postoperative ECG abnormalities [median (IQR) 50.5 (31.0–103.6) vs 22.5 (11.1–49.0) pg ml⁻¹ (P=0.01)] and in patients who had either elevation of cTnI >0.32 ng ml⁻¹ or postoperative ECG abnormalities [50.4 (30.4–93.7) vs 21.5 (10.5–46.9) pg ml⁻¹ (P<0.001)]. A preoperative BNP >40 pg ml⁻¹ was associated with a five-fold increase in the risk of developing either postoperative cTnI elevation >0.32 ng ml⁻¹ or new ECG abnormalities (OR 5.3, 95% CI 2.2–13.1, P<0.001).

Use of a lower cut-off level of cardiac troponin I

Twenty-seven patients had a cTnI level >0.1 ng ml⁻¹ at 24 and 72 h, of whom one died. BNP predicted cTnI
BNP and outcome of major non-cardiac surgery

Table 1 Baseline patient characteristics. Data are expressed as number (percentage) except where otherwise indicated. Myocardial damage was defined as postoperative cTnI > 0.32 ng ml⁻¹ within 72 h of surgery. Cardiac medication was defined as the regular prescription of a medication for a cardiovascular disease. Prior revascularization was defined as a history of coronary revascularization for angina or myocardial infarction. Postoperative ECGs were not recorded at all time points in 10 patients (none with cTnI levels > 0.32 ng ml⁻¹). Optimal cut-off as defined by ROC curve

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Total cohort (n=204)</th>
<th>Patients with perioperative death or myocardial damage (n=12)</th>
<th>Patients without perioperative death/myocardial damage (n=192)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>125 (61)</td>
<td>7 (58)</td>
<td>118 (61)</td>
<td>1.00</td>
</tr>
<tr>
<td>Age mean (range)</td>
<td>66 (28–79) yr</td>
<td>70 (57–84) yr</td>
<td>66 (28–100) yr</td>
<td>0.19</td>
</tr>
<tr>
<td>Any cardiac medication</td>
<td>108 (53)</td>
<td>9 (75)</td>
<td>99 (52)</td>
<td>0.14</td>
</tr>
<tr>
<td>Use of β-blockers</td>
<td>42 (21)</td>
<td>3 (25)</td>
<td>39 (20)</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (15)</td>
<td>2 (17)</td>
<td>28 (15)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>74 (36)</td>
<td>6 (50)</td>
<td>68 (35)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior myocardal infarction</td>
<td>20 (10)</td>
<td>1 (8)</td>
<td>19 (10)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior angina</td>
<td>47 (23)</td>
<td>3 (25)</td>
<td>44 (23)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior atrial fibrillation</td>
<td>7 (3)</td>
<td>1 (8)</td>
<td>6 (3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Smoker</td>
<td>48 (23)</td>
<td>3 (25)</td>
<td>45 (23)</td>
<td>1.00</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>12 (6)</td>
<td>1 (8)</td>
<td>11 (6)</td>
<td>0.53</td>
</tr>
<tr>
<td>Any known cardiac disease</td>
<td>49 (24)</td>
<td>3 (25)</td>
<td>46 (24)</td>
<td>1.00</td>
</tr>
<tr>
<td>Creatinine mean (SD)</td>
<td>96 (21) µmol ml⁻¹</td>
<td>95 (15) µmol ml⁻¹</td>
<td>96 (22) µmol ml⁻¹</td>
<td>0.81</td>
</tr>
<tr>
<td>Revised Cardiac Risk Index ≥ 2</td>
<td>65 (32)</td>
<td>5 (42)</td>
<td>60 (31)</td>
<td>0.53</td>
</tr>
<tr>
<td>Significant postoperative ECG changes</td>
<td>14 (7)</td>
<td>1 (8)</td>
<td>13 (7)</td>
<td>0.60</td>
</tr>
<tr>
<td>BNP median (IQR)</td>
<td>26.6 (11.5–50.3) pg ml⁻¹</td>
<td>52.2 (30.4–96.4) pg ml⁻¹</td>
<td>22.2 (11.2–48.8) pg ml⁻¹</td>
<td>0.01</td>
</tr>
<tr>
<td>BNP &gt; 40 pg ml⁻¹</td>
<td>68 (33)</td>
<td>9 (75)</td>
<td>59 (31)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 2 Surgical groups and prevalence of perioperative death or acute myocardial infarction (defined as postoperative cTnI > 0.32 ng ml⁻¹ within 72 h of surgery) according to the type of surgery

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Number of patients</th>
<th>Number with postoperative myocardial damage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major vascular surgery</td>
<td>70</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Major abdominal surgery</td>
<td>84</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Major pelvic surgery</td>
<td>50</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>204</td>
<td>12 (6)</td>
</tr>
</tbody>
</table>

elevation >0.1 ng ml⁻¹ or death (P=0.008). A BNP > 40 pg ml⁻¹ also predicted this outcome (OR 3.5, 95% CI 1.5–8.0, P=0.003).

BNP levels and postoperative hospital stay

Patients with preoperative BNP levels > 40 pg ml⁻¹ remained in hospital after operation for a median (IQR) of 12 (7–19) days compared with 9 (7–12) days in those with preoperative BNP ≤40 pg ml⁻¹ (P=0.006).

Discussion

We have demonstrated that preoperative BNP levels are predictors of perioperative death or acute myocardial injury in patients undergoing major non-cardiac surgery. Using a cut-point of 40 pg ml⁻¹ for preoperative BNP differentiates patients with an almost seven-fold increased risk of cardiac events in the early postoperative period. A preoperative BNP above this cut-off point was also associated with an increased postoperative hospital stay.

Despite being unable to demonstrate a relationship between new ECG changes and cTnI elevation, we have shown that preoperative BNP levels were higher in patients who exhibited postoperative ECG abnormalities and in patients who had either elevated cTnI or postoperative ECG abnormalities. The study was not powered to assess the ability of BNP levels to predict death alone after surgery.

Alternative methods of determining perioperative cardiac risk

Efforts to identify patients at increased cardiac risk when undergoing non-cardiac surgery have led to the development of a variety of scoring systems.¹⁻³ ⁶ The quoted utility of these indices varies, depending on the system, the patient population being studied, and the end-points used. In a multi-centre study comparing several of these risk stratification tools, the areas under the ROC curves ranged from 0.60 to 0.64.²⁷ Lee and colleagues³ quote an area under the ROC curve of 0.76 for the Revised Cardiac Risk Index’s ability to identify patients who develop a postoperative cardiac event. The Revised Cardiac Risk Index was, however, derived and validated in patients aged 50 yr or over, who have an increased likelihood of developing a postoperative cardiac event. The definition of these events was also broader, including pulmonary oedema, ventricular fibrillation and complete heart block, and acute myocardial infarction (using a less contemporary definition than our own). These differences may explain the relatively poor performance of the Index in the current cohort. Most probably, however, this relates to the relative homogeneity of the current cohort in terms of their clinical risk score. Such factors make it difficult to draw direct
comparisons between the current cohort and previous studies. Nevertheless, our data do suggest BNP may have a useful role in risk prediction in this setting. We recognize, however, that the confidence interval around the area under the ROC curve value of 0.72 is wide (0.59–0.86), and larger studies are required to provide more precise estimates.

**Potential advantages of B-type natriuretic peptide**

The use of a biochemical test for risk stratification has several advantages. It requires only a single and relatively inexpensive blood test. This is widely available on existing clinical biochemistry analysers and is routinely performed in many hospitals. Indeed, BNP levels can now be accurately obtained using ‘point-of-care’ assays at the bedside. In addition, a biochemical test avoids the difficulties inherent in applying complex scoring systems to individual patients and provides an objective measure, without the potential for subjective interpretation of clinical parameters. A clearly defined ‘cut-off point’, such as the 40 pg ml\(^{-1}\) derived from our ROC curve analysis, would be simple to use in a clinical setting.

**Previous studies**

Yeh and colleagues\(^\text{16}\) have recently demonstrated that NT-proBNP predicted a composite end-point of ‘post-operative cardiac complications’ in 190 patients undergoing non-cardiac surgery. This important study does, however, have some limitations. In particular, it was retrospective and used several subjective end-points. Indeed, 11 of the 15 end-points in this cohort were the occurrence of postoperative cardiac failure—a diagnosis that is extremely difficult to establish, particularly when this was not addressed systematically or prospectively. In contrast, our
study was prospective and used an objective primary end-point. More recently, Berry and colleagues\(^1\) have reported that in a cohort of 41 patients undergoing major vascular surgery, preoperative plasma BNP levels were increased in those suffering perioperative myocardial infarction (n=11). These studies, in conjunction with the current data, suggest that BNP and NT-proBNP may play a role in preoperative risk stratification. However, further studies are required to determine optimum cut-offs in differing patient populations. Likewise, it is important to recognize that the prognostic information obtained from measurement of BNP remains imperfect. Knowledge of levels might perhaps improve the predictive accuracy of existing methods—such that a strategy combining simple clinical parameters and BNP will be the most appropriate. Recent data derived from the Heart Outcomes Prevention Evaluation (HOPE) Study suggest that NT-proBNP levels convey significant additional prognostic information to conventional risk factors among patients with documented atherosclerotic disease or diabetes mellitus.\(^2\)

**Clinical implications**

The American Heart Association/American College of Cardiology Guidelines Update on Perioperative Cardiovascular Evaluation for Non-cardiac Surgery\(^3\) suggests that preoperative risk assessment should consider the patients’ risk, their functional capacity, and the surgical risk in a complex algorithm system designed to guide preoperative investigation and treatment. A simple test such as BNP might represent a cost-effective way of assisting in the identification of patients who would benefit from more intensive, and costly, preoperative testing and facilitate targeted interventions that may reduce morbidity and mortality. These include the optimization of preoperative fluid balance and perioperative beta blockade.\(^4\)\(^\,\)\(^5\)\(^\,\)\(^6\) Further work is, however, required to clarify the utility of BNP in this role.

**Choice of end-points**

With the advent of cTn measurement, the definition of myocardial infarction has changed and the diagnosis requires evidence of myocardial necrosis demonstrated by a clear rise in levels of a specific biomarker (such as cTnI or cTnT).\(^7\)\(^\,\)\(^8\) Ideally, the diagnosis requires typical chest pain or ECG changes. However, perioperative myocardial infarction is often silent or associated with atypical clinical signs and symptoms. In addition, ECG changes in this setting are often non-specific.\(^9\)\(^\,\)\(^10\) To avoid subjectivity in this regard, we used biochemical evidence of cardiac injury as a robust and objective end-point. Specifically, we assayed cTnI, collected on every patient at defined time points. Previous data have confirmed that minor cTn release in this setting is associated with a much poorer medium term outcome.\(^11\) However, the threshold of cTnI used to diagnose myocardial injury or infarction is controversial, and may have a considerable impact on the results. We prospectively decided to use the generally recommended cut-off for diagnosing myocardial infarction.\(^12\)–\(^15\) Widening the definition in secondary analysis to include ECG changes showed broadly similar results. Likewise, the use of a lower threshold for cTnI (>0.1 ng ml\(^{-1}\)) produced similar results.

The main weakness of this study is the low incidence of perioperative death and acute myocardial injury—limiting its power. In addition, we have studied the prognostic utility of BNP in a heterogeneous cohort of patients undergoing a variety of major surgical procedures. Ideally, these results should be repeated in a study powered to detect objective primary outcomes in all appropriate surgical subgroups. Likewise, further work should determine the utility of BNP in combination with existing risk stratification tools and, more importantly, assess whether interventions that reduce BNP levels preoperative can prevent perioperative complications. Until such data are available the precise role of BNP in this setting remains unclear.

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