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**THE UTILITY OF B-TYPE NATRIURETIC PEPTIDE IN PREDICTING POST-OPERATIVE CARDIAC EVENTS AND MORTALITY IN PATIENTS UNDERGOING MAJOR EMERGENCY NON-CARDIAC SURGERY.**

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## **ABSTRACT**

B-type natriuretic peptide (BNP) levels predict cardiovascular risk in several settings. We hypothesized that they would identify individuals at increased risk of complications and mortality following major emergency non-cardiac surgery. Forty patients were studied with a primary end-point of a new post-operative cardiac event, and/or development of significant ECG changes, and/or cardiac death. The main secondary outcome was all cause mortality at 6 months. Pre-operative BNP levels were higher in 11 patients who suffered a new post-operative cardiac event ( $p=0.001$ ) and predicted this outcome with an area under the receiver operating characteristic curve of 0.85 (CI=0.72-0.98,  $p=0.001$ ). A pre-operative BNP value  $>170\text{pg}\cdot\text{ml}^{-1}$  has a sensitivity of 82% and a specificity of 79% for the primary end-point. In this small study, pre-operative BNP levels identify patients undergoing major emergency non-cardiac surgery who are at increased risk of early post-operative cardiac events. Larger studies are required to confirm these data.

Word count -148

## **KEYWORDS**

B-type natriuretic peptide, non-cardiac surgery, emergency surgery, risk stratification

Major emergency surgery is associated with high levels of morbidity and mortality [1,2]. The mortality from emergency laparotomy in the UK may be as high as 25% [3] and in our hospital carries a 12% risk of death [4]. Likewise, major emergency hip surgery is associated with a mortality of 9% at 30 days and 22% at 120 days [5]. Mortality in this setting may relate to the effects of the underlying condition or to direct effects of surgery. However, the majority of patients die due to the development of major cardiac complications in the early post-operative period [1,2].

Accurate pre-operative risk stratification is important for several reasons. It allows clinicians to explain and quantify risk and, thus, is an essential component in gaining informed consent. Perhaps more importantly, accurate identification of patients at highest risk might allow targeting of interventions that may improve outcome in elective or emergency surgery, such as peri-operative beta blockade and pre-operative optimisation [6-8]. Predicting outcome in emergency surgery is, however, difficult - particularly as existing risk assessment tools were developed and evaluated in patients undergoing major elective non-cardiac surgery and may lack accuracy in predicting the development of cardiac complications in other settings [6,9-11]. In addition, alternate methods of assessing cardiovascular risk - such as stress testing and/or echocardiography - may be impractical or difficult. The availability of a readily available 'biomarker' that might assist with risk stratification would, therefore, be of particular value in this situation.

B-type natriuretic peptide (BNP) is secreted chiefly from the left ventricle in response to filling pressure and volume load. It promotes natriuresis, diuresis and vasodilatation [12]. Blood concentrations of BNP are raised in patients with

cardiac disease, particularly those with heart failure, though also in response to ischaemia. They are important markers of cardiovascular prognosis in many settings [13,14]. In particular, recent research suggests that pre-operative BNP levels are predictive of post-operative cardiac complications in patients following coronary artery bypass grafting [15,16]. They may also have a place in risk prediction before major elective non-cardiac surgery [17-20]. The utility of BNP in the risk stratification of patients undergoing emergency surgery has not, however, been previously tested. We hypothesised that pre-operative BNP would predict peri-operative myocardial events and / or death after surgery in patients undergoing major emergency non-cardiac surgery.

## **METHODS**

The research 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 emergency major non-cardiac surgery. Major emergency non-cardiac surgery was defined as emergency laparotomy for gastrointestinal pathology and emergency hip surgery for fractured neck of femur. Emergency surgery was defined as surgery that requires to be performed within 24 hours of presentation. Pre-operative BNP sampling was undertaken after completion of pre-operative fluid and electrolyte resuscitation immediately before surgery.

### ***Data collection***

Pre-operative data collection included the recording of a 12 lead electrocardiogram (ECG), patient demographics, medical and surgical history, pre-operative medications, renal and hepatic function. Pre-operative blood

samples were also obtained for cardiac troponin I (cTnI) and plasma BNP levels. The Revised Cardiac Risk Index (RCRI), American Society Anesthesiology (ASA) score, pre-morbid New York Heart Association functional class and Canadian Cardiovascular Society angina score were calculated. Intra-operative data collection included details of surgery and anaesthesia, cardiac and non-cardiac complications and intra-operative inotrope requirement. Post-operative data collection included the recording of a 12 lead ECG and measurement of cTnI levels at 24 and 72 hours after surgery. Patients were followed-up while in hospital and vital status determined at 6 months using data provided by the General Register Office for Scotland.

All patients were followed up by an investigator who was unaware of the patient's biochemistry results and ECG outcomes. Electrocardiograms were analyzed by a consultant cardiologist blinded to all other data including the patient's 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.

### ***Study end-points***

The primary endpoint was the predictive power of BNP for a major adverse post operative cardiac event. This was defined as: cardiac death during the index admission *and/or* new post-operative myocardial injury (cTnI  $\geq 0.1\text{ng.ml}^{-1}$  at 24 and/or 72 hours with undetectable pre-operative levels) *and/or* the development of clinically significant new post-operative ECG changes, within 72 hours of surgery.

We have used the terminology myocardial 'injury' instead of 'infarction' as the latter is difficult to define in this setting [21-29]. For the purposes of this study acute peri-operative myocardial injury was defined as evidence of myocardial cell necrosis (cTnI  $\geq 0.1 \text{ ng.ml}^{-1}$  – the local lower limit of detection of the assay used). Clinically significant ECG changes were prospectively defined as-

- a) the development of changes suggestive of significant acute myocardial ischemia / infarction: the development of new, post-operative, T-wave inversion  $\geq 2 \text{ mm}$  and / or ST segment deviation  $\geq 2 \text{ mm}$  in at least two-contiguous chest leads or 1mm in at least two contiguous limb leads and / or
- b) the development of new sustained abnormal cardiac rhythm within 72 hours of surgery.

The following secondary end-points were also assessed:

- a) new post-operative myocardial injury (defined as above), within 72 hours of surgery
- b) any post-operative myocardial injury (cTnI  $\geq 0.1 \text{ ng.ml}^{-1}$  at 24 and/or 72 hours regardless of pre-operative levels)
- c) all-cause mortality 6 months after surgery

### **Assays**

Blood was collected in EDTA and lithium heparin Vacutainer™ tubes, which were then immediately centrifuged with plasma stored at  $-80^{\circ}\text{C}$  for later analysis.

Prior to the pre-operative blood sample, patients were asked to lie quietly in the supine position for 30 minutes 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 analyser [30,31]. The

lower limit of detection for BNP is  $2\text{pg.ml}^{-1}$  and the coefficients of variation at  $29.4\text{pg.ml}^{-1}$  and  $410\text{pg.ml}^{-1}$  are 4.7% and 2.8% respectively [30,31].

## **Statistics**

Data was analysed on Statistics Package for Social Sciences™ 12 software. Categorical data are presented as absolute values and percentages. Normally distributed continuous variables are expressed as mean and standard deviation, while those with a skewed distribution are expressed as median and interquartile range. Fisher's exact test was used to test differences between independent categorical data. Differences between two independent groups of continuous data were tested using the Mann-Whitney *U* test. Receiver Operating Characteristic curves were plotted and the area under the curve estimated. Backward conditional logistic regression analysis was used to test the independent predictive value of elevated BNP levels. A *p* value  $<0.05$  was considered significant.

## **RESULTS**

Fifty-eight patients met inclusion criteria for the study and were invited to participate. Forty-six patients (79%) consented to the study and 40 underwent surgery and completed the trial protocol. Baseline data are presented in table 1.

The median pre-operative BNP level was  $100\text{pg.ml}^{-1}$  (62-205), rising at 24 hours to  $157\text{pg.ml}^{-1}$  (82-225:  $p=0.07$  v baseline) and falling by 72 hours post-operatively to  $72\text{pg.ml}^{-1}$  (41-167:  $p=0.001$  v baseline). Fifteen patients had detectable ( $\geq 0.1\text{ng.ml}^{-1}$ ) levels of cTnI pre-operatively. In six of these subjects levels fell below  $0.1\text{ng.ml}^{-1}$  post-operatively, whereas an additional 5 patients

exhibited *de novo* elevation. Six further patients developed significant new changes on their post-operative ECG(s). One patient died 4 days after surgery due to acute myocardial infarction, there were no other deaths within the first 28 days. A further 5 patients died during follow-up, resulting in a total of 6 deaths (15%) at 6 months.

Pre-operative BNP levels in patients were significantly higher among patients who experienced a post-operative cardiac event (table 1 and figure 1). Patients who exhibited new post-operative myocardial damage (elevation of cTnI  $\geq 0.1 \text{ ng.ml}^{-1}$  at 24 and/or 72 hours with normal pre-operative levels: n=5) had a median pre-operative BNP of  $201 \text{ pg.mL}^{-1}$  (135-407) compared to  $88 \text{ pg.mL}^{-1}$  (59-194) in patients without *de novo* cTnI release (p=0.07). Likewise, median pre-operative BNP levels among patients with any post-operative myocardial damage (cTnI  $\geq 0.1 \text{ ng.ml}^{-1}$  at 24 and/or 72 hours regardless of pre-operative levels: n=14) were  $214 \text{ pg.mL}^{-1}$  (89-433) compared to  $83 \text{ pg.mL}^{-1}$  (52-144; p=0.005) among those patients who did not have any cTnI elevation after surgery.

Median pre-operative BNP levels were  $196 \text{ pg.mL}^{-1}$  [96-296] in the 6 patients who died during 6 month follow-up (v  $88 \text{ pg.mL}^{-1}$  [57-201] among survivors: p=0.10). Pre-operative cTnI levels were  $0.00 \text{ ng.mL}^{-1}$  [0.00-0.13] in surviving patients (v  $0.1 \text{ ng.mL}^{-1}$  [0.00-0.52] in those that died) (p=0.38). However, neither elevated ( $\geq 0.1 \text{ ng.ml}^{-1}$ ) pre-operative or post-operative cTnI levels predicted 6-month mortality (p=0.65 for both).

Pre-operative BNP predicted the primary outcome with an area under the receiver operator characteristic curve of 0.85 (95% confidence interval [CI] 0.72-

0.98,  $p=0.001$ ). The optimal cut-point derived from this curve was  $170\text{pg.mL}^{-1}$ . This has a sensitivity of 82% and a specificity of 79% (Figure 2). Pre-operative BNP levels  $\geq 170\text{pg.mL}^{-1}$  predicted the primary outcome with an odds ratio (OR) of 17.3 (95% CI 2.9-101.9,  $p=0.002$ ).

### **Relative utility of BNP and existing risk prediction scores**

Patients with an RCRI of 1 or 2 had a BNP of  $83\text{pg.mL}^{-1}$  (56–191) compared to  $195\text{pg.mL}^{-1}$  (121–466:  $p=0.02$ ) in those with a RCRI of 3 and 4. Likewise, patients with ASA scores of 1 and 2 had a median BNP of  $83\text{pg.mL}^{-1}$  (63–154) compared to  $183\text{pg.mL}^{-1}$  (60–356:  $p=0.12$ ) in those with an ASA score of 3 to 5.

When pre-operative BNP levels (as a continuous variable) were included in a multivariable model along with the pre-operative ASA score and the RCRI the only independent predictor of the primary outcome was the ASA score (OR 4.78 per unit increase, 95% CI 1.48-15.39,  $p=0.009$ ). There was, however, a trend for BNP to provide additional independent prognostic information (OR 1.04 per  $10\text{pg.mL}^{-1}$  increase, 95% CI 1.00-1.08,  $p=0.07$ ). In a second model including the ASA score, the RCRI and BNP levels dichotomised around the optimal cut-off, the independent predictors were BNP  $\geq 170\text{pg.mL}^{-1}$  (OR 13.6, 95% CI 1.9-97.8,  $p=0.009$ ) and the RCRI (OR 2.8 per unit increase, 95% CI 1.2-6.9,  $p=0.02$ ).

## **DISCUSSION**

Patients undergoing major emergency surgery are at high risk of peri-operative cardiovascular complications. However, within this population the magnitude of this hazard will vary. Paradoxically, these patients are least likely to undergo formal risk-stratification. This, at least in part, reflects the imperative for surgery and the absence of evidence-based interventions to reduce complications. It may also be due to the difficulty in performing specialist investigations, plus the lack of well-validated and easily applied methods of estimating risk in this setting. Some of these reasons, in turn, reflect the paucity of research in such acutely ill-patients - who are less easy to identify and enrol into trials than those undergoing elective surgery.

The current study suggests that pre-operative BNP levels are higher in patients who suffer an early post-operative cardiac event and may provide prognostic information that is incremental to existing methods of risk-prediction such as the ASA score and the RCRI. Pre-operative BNP also shows a trend towards predicting 6-month mortality.

### **Prior studies**

There are no prior data addressing the role of BNP in predicting outcome from emergency non-cardiac surgery. However, several recent reports have suggested that BNP or N terminal pro-BNP levels are useful in pre-operative risk-stratification in elective non-cardiac surgery [17-19]. In this setting BNP and N terminal pro-BNP identify patients at risk of per-operative myocardial damage and heart failure. In addition, BNP predicts medium term mortality in this group [20]. There is also a growing body of literature suggesting a prognostic role for

BNP and its derivatives at the time of cardiac surgery [15,16]. In contrast, the role of BNP in predicting risk associated with critical illness is less clear [32-34].

There are a variety of mechanisms whereby BNP might predict risk in this setting. BNP is often considered a global marker of cardiac function or health. In patients with symptomatic heart disease natriuretic peptide levels are markers of increased myocardial stress, usually from volume and pressure overload but also in response to hypoxia and ischaemia [35,36]. Levels of BNP predict cardiac events, such as incident myocardial infarction and death, in many settings - including patients with heart failure, stable coronary heart disease and even in apparently healthy populations [14]. Many patients presenting for major surgery may have clinical or subclinical cardiac failure or ischaemic heart disease. Pre-operative BNP levels will reflect their underlying cardiovascular status, identifying those with a reduced cardiac reserve - who present a greater risk of peri-operative myocardial infarction and early and late mortality [37-39].

### **Other methods of risk stratification**

The practicalities of risk-stratification in emergency surgery have been mentioned above. Existing risk prediction scores such as the ACC/AHA and Revised Cardiac Risk Index have limited clinical utility and are not commonly applied in everyday practice [9-11]. Further, these scores may have a limited role in emergency surgery patients as they have been derived in cohorts undergoing elective major non-cardiac surgery. Given these limitations, a rapid and relatively cheap biochemical test, potentially available by near patient testing, with a clearly defined cut point, would be of considerable clinical utility.

## **Limitations**

This was a small study with limited power. In addition, the requirement to gain informed consent meant that patients with low mental state questionnaire scores were excluded. As these patients often have the highest operative risk, this may have introduced a degree of bias into our sample. Acute illness and fluid imbalance may also affect BNP levels. We attempted to allow for this by measuring BNP after pre-operative resuscitation was complete. However this time point is imprecise and the exact fluid status of the patient at time of sampling is uncertain. Finally, our cohort is heterogenous - including patients undergoing major emergency abdominal and hip surgery. Nevertheless, if BNP levels were to prove clinically useful they would have to demonstrate sensitivity and specificity in such diverse clinical situations.

In a small study we were able to show that elevated pre-operative BNP levels were associated with an increased risk of early post-operative cardiac events in patients undergoing major emergency non-cardiac surgery. Further work is required to clarify the role of BNP in this setting.

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**Table 1.** Baseline clinical characteristics of the study cohort.

	<b>Patient Characteristic</b>	<b>Patients with post-operative cardiac event* (n = 11)</b>	<b>Patients without post-operative cardiac event* (n = 29)</b>	<b>P- value</b>
Male	15 (38)	3 (27)	12 (41)	0.48
Age	74 (64-83)	80 (69-85)	73 (62-80)	0.08
Diabetes	4 (10)	3 (27)	1 (3)	0.06
Hypertension	20 (50)	8 (73)	12 (41)	0.08
Previous MI	8 (20)	6 (55)	2 (7)	0.003
MI <6 months ago	0	0	0	-
Angina	9 (23)	5 (45)	4 (14)	0.05
Atrial fibrillation	4 (10)	0	4 (14)	0.26
Current smoker:	11 (28)	1 (9)	10 (35)	0.11
Previous CABG or PCI	5 (13)	3 (27)	2 (7)	0.12
Previous major non-cardiac surgery	12 (30)	4 (36)	8 (28)	0.43
Cardiac medication	23 (58)	9 (82)	14 (48)	0.06
Chronic beta blockade	8 (20)	3 (27)	5 (17)	0.38
Peri-operative beta blockade	0	0	0	-
CCS angina status	0.48 ±1.01	1.09 ±1.51	0.24 ±0.64	0.03
NYHA functional class	1.23 ±0.58	1.55 ±0.93	1.10 ±0.31	0.12
RCRI score	1.68 ±1.02	2.55 ±1.29	1.34 ±0.67	0.004
ASA score	2.70 ±0.88	3.45 ±0.82	2.41 ±0.73	0.001
Creatinine (µmol/L)	85 (69-107)	87 (69-179)	84 (69-104)	0.29
BNP (pg.ml <sup>-1</sup> )	100 (62-205)	310 (177-443)	82 (51-149)	0.001
cTnI (ng.ml <sup>-1</sup> )	0.00 (0.00-0.16)	0.12 (0.10 - 0.43)	0.00 (0.00- 0.12)	0.13
<b>Surgical procedure</b>				

Hip surgery	23	7	16	
Laparotomy	17	4	13	0.73
<b>Anaesthesia</b>				
General <sup>†</sup>	25	7	18	
Regional <sup>†</sup>	13	4	9	1.00

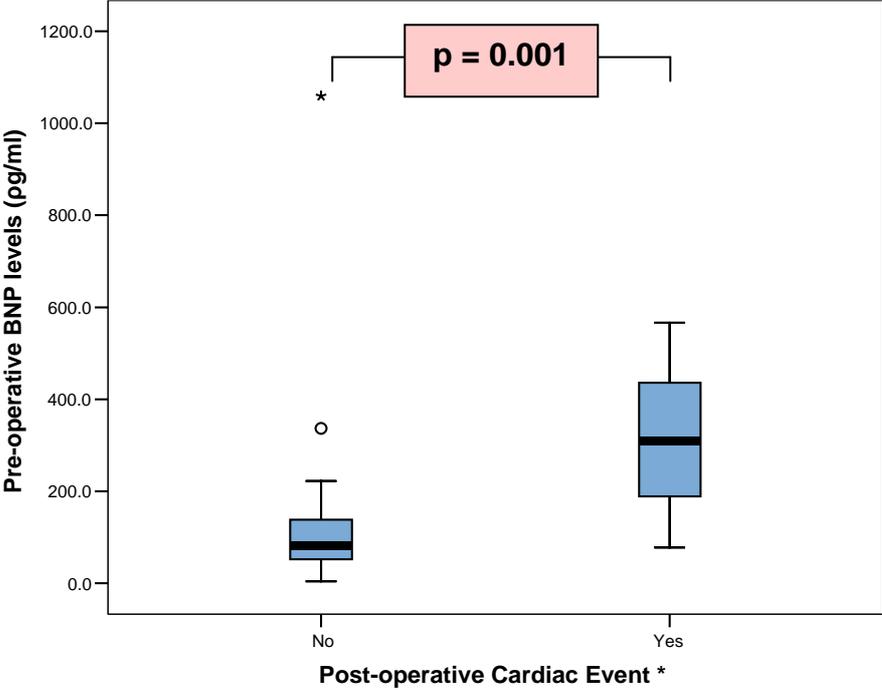
Variables presented as medians and interquartile ranges or as number and percentages.

\* post-operative cTnI  $\geq 0.10\text{ng.ml}^{-1}$  (where pre-operative cTnI  $< 0.10\text{ng.ml}^{-1}$ ), and/or development of significant ECG changes (see text for details), and/or death.

<sup>†</sup> two patients had both regional and general anaesthesia

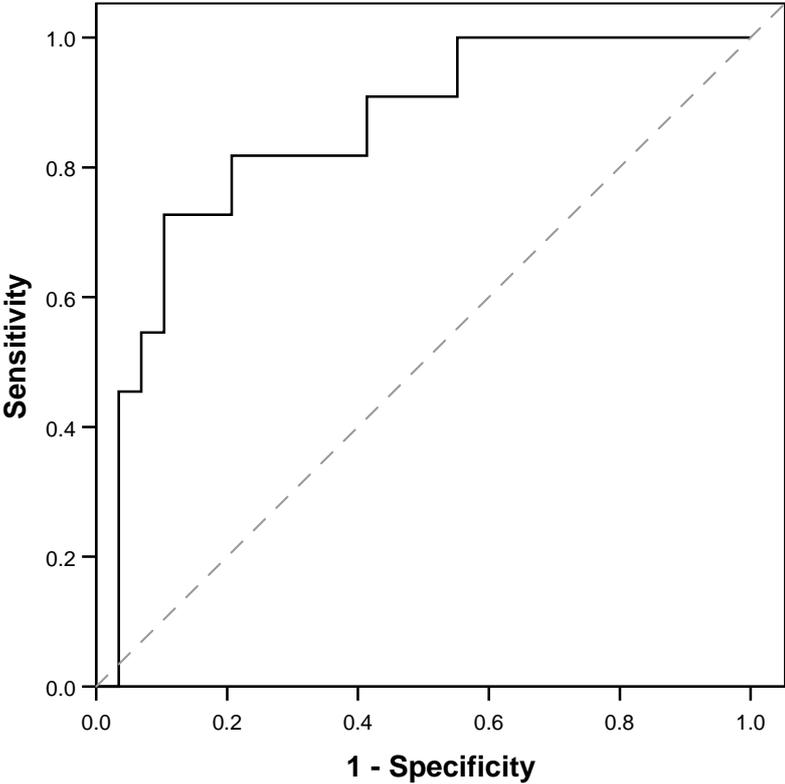
MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; RCRI = revised cardiac risk index; ASA = American Society of Anesthesiologists grading; BNP = B-type natriuretic peptide; cTnI = cardiac troponin I.

**Figure 1.** A comparison of pre-operative BNP levels in patients who experienced a post-operative cardiac event against those who did not.



Central lines represent medians, boxes 25<sup>th</sup> and 75<sup>th</sup> centiles and whiskers represent ranges.

**Figure 2.** Receiver operator characteristic curve for pre-operative BNP levels predicting an early post-operative cardiac event.



Area under the curve = 0.85 (95% CI=0.72-0.98, p=0.001).