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Brain natriuretic peptide is a good predictor for outcome in cardiac surgery

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Background and aim: The heart secretes brain natriuretic peptide (BNP) in response to myocardial stretch. The aim of this study was to determine whether adverse effects after cardiac surgery were associated with higher serum BNP levels pre-operatively.
Methods: One hundred and thirty-five patients undergoing various cardiac procedures were included in the study, and N-terminal pro-BNP (NT-pro-BNP) was measured pre-operatively. Post-operative complications were defined as follows: (i) a post-operative length of stay in the intensive care unit (ICU) exceeding 48 h; (ii) mortality at 28 days; (iii) the need for inotropic agents and/or intra-aortic balloon pump (IABP); and (iv) renal failure. Serum NT-pro-BNP values were compared for patients with and without complications. The serum NT-pro-BNP level was also correlated with the euroSCORE and ejection fraction (EF).
Results: Pre-operative serum NT-pro-BNP levels were significantly higher in patients with an ICU length of stay of more than 2 days or death prior to post-operative day 28 (3118 ng/l vs. 705 ng/l; $P < 0.001$). Pre-operative serum NT-pro-BNP levels were also significantly higher in patients needing inotropic agents (2628 ng/l vs. 548 ng/l; $P < 0.001$) or IABP insertion (3705 ng/l vs. 935 ng/l; $P = 0.001$) or developing renal failure (2857 ng/l vs. 945 ng/l; $P < 0.001$) post-operatively. The correlation between the serum NT-pro-BNP level and euroSCORE was good ($r = 0.658$; $P < 0.001$). The receiver operating characteristic (ROC) curves were used to assess the ability of serum NT-pro-BNP, euroSCORE and EF to predict outcome after cardiac surgery. This revealed an area under the ROC curve for the length of stay in the ICU or mortality at 28 days of 0.829 for serum NT-pro-BNP, 0.814 for euroSCORE and 0.328 for EF assessed by transesophageal echocardiography, indicating that the pre-operative serum NT-pro-BNP level is a good prognostic indicator for outcome after cardiac surgery.
Conclusion: Serum NT-pro-BNP is a good predictor for complications after cardiac surgery, and is as good as euroSCORE and better than EF.

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Key words: Adverse outcome; brain natriuretic peptide; cardiac surgery; euroSCORE.

As the age of patients undergoing cardiac surgery increases, the number of those with comorbid illness and the number of complex procedures also increase (1). In the USA, coronary artery bypass grafting (CABG) procedures have an average mortality of 2.7% (2) and the overall 30-day mortality for cardiac surgery is 3.2% (1). The most common complications of cardiac procedures are death, myocardial infarction (MI), stroke, infections, prolonged ventilator support and renal failure (3). It is important for surgical and intensive care physicians to identify those patients at increased risk of complications, so that resource management can be planned and patients can be informed about the risk of surgery.

The cardiac hormone brain natriuretic peptide (BNP) is secreted mainly from the cardiac ventricles in response to myocardial stretch as a result of volume overload, e.g. in heart failure (4). It has also been shown that BNP is released when there is increased blood volume secondary to increased sodium intake (5), with a brief period of ischemia (6), and that several endogenous substances, e.g. norepinephrine, angiotensin II and endothelin 1, increase the release of BNP (7, 8). Natriuretic peptide receptors (NPRs) are located in the kidneys, arteries, veins, adrenal glands and ventricles of the heart (9). When BNP binds to its receptors, it causes an increase in intracellular cyclic guanosine 3′,5′-monophosphate (cGMP), leading to its biological effect. The main effects of BNP are diuresis, natriuresis, and arterial and venous dilatation (10). BNP also inhibits cardiac hypertrophy and fibroblast formation (11, 12) and decreases diastolic velocity (13).

Multiple scoring systems have been developed to evaluate the risk of cardiac surgery. One of these is euroSCORE. The euroSCORE scoring system predicts mortality based on many factors. The logistic euroSCORE calculates the predicted mortality in percentage points by assigning a weight to each factor (see the euroSCORE homepage: www.euroscore.org). However, studies have shown that there is a tendency to overestimate a patient's risk of death using euroSCORE (14, 15).

The aims of this study were to determine whether post-operative complications after cardiac surgery were correlated with elevated pre-operative serum N-terminal pro-BNP (NT-pro-BNP) levels, and to compare the utility of serum NT-pro-BNP, ejection fraction (EF) evaluated by transesophageal echocardiography (TEE) and euroSCORE as predictors of complications after cardiac surgery.

Materials and methods

This study was approved by the hospital's ethics committee. It included 135 patients [102 men (75.6%) and 33 women (24.4%)] undergoing cardiac surgery: conventional CABG (75 patients, 56%), off-pump coronary artery bypass (OPCAB) (17 patients, 12%), valve repair (16 patients, 12%) or both CABG and valve repair (27 patients, 20%). All patients were undergoing elective cardiac surgery considering the criteria on the euroSCORE homepage (www.euroscore.org) for emergency surgery. Data were collected from hospital records of 179 patients and the pre-operative serum NT-pro-BNP levels were available for 135 patients (75.4%). Pre-operative data collection included: EF evaluated with TEE after induction of anesthesia and the data needed to calculate euroSCORE: (i) age; (ii) gender; (iii) chronic pulmonary diseases; (iv) extra-cardiac arteriopathy; (v) neurological dysfunction; (vi) previous cardiac surgery; (vii) creatinine > 200 μmol/l; (viii) endocarditis; (ix) critical pre-operative state; (x) unstable angina; (xi) left ventricular function; (xii) recent MI; (xiii) pulmonary hypertension; (xiv) emergency; (xv) other than isolated CABG; (xvi) surgery on the thoracic aorta; and (xvii) post-infarct septal rupture (see www.euroscore.org) (16). Post-operative data collection included the length of stay in the intensive care unit (ICU), mortality at 28 days and the need for inotropic agents and/or intra-aortic balloon pump (IABP) support. The patients were divided into two groups: those with and without post-operative complications. Post-operative complications were defined as a length of stay in the ICU for more than 2 days and/or mortality at 28 days. Pre-operative NT-pro-BNP levels were compared between the two groups. The NT-pro-BNP levels were also compared in patients who did or did not require inotropic agents and/or IABP support more than 24 h after surgery, and in those who did or did not experience post-operative MI or renal failure. Post-operative MI was defined as serum creatine kinase MB (CK-MB) levels higher than 70 μg/l within 1 week of surgery. Renal failure was defined as more than a 50% increase in serum creatinine levels after surgery compared with pre-operative levels. Serum NT-pro-BNP was also compared with the logistic euroSCORE and pre-operative EF as prognostic indicators of outcome. In our calculation of euroSCORE, a different definition of unstable angina than cited in the guidelines was used (16). It was defined as resting angina needing nitrates, including long-acting nitrates, until arrival in the operating room. This was a result of the clinical practice in our hospital of treating unstable angina with oral long-acting nitrates in preference to intravenous nitroglycerine. Strict adherence to the definition on the euroSCORE homepage (www.euroscore.org) would have given our patients a lower risk of mortality than calculated here.

Blood was collected in serum tubes. NT-pro-BNP was measured pre-operatively and CK-MB was measured daily for 7 days post-operatively. The measurement of NT-pro-BNP was performed using electrochemical luminescence immunoassay (ECLIA) in a Roche Elecsys 1010/2010 (Roche, Basel, Basel-Stadt, Switzerland). The coefficient of variation for this method is 2.2–3.2%. The detection range is 5–35,000 ng/l (17).

Statistical analysis

Data were analyzed using SPSS software (version 11.0.0, SPSS Inc., Chicago, IL). Data were expressed as the mean with 95% confidence interval (CI), or median. Comparisons of pre-operative NT-pro-BNP levels between different groups were made by the non-parametric Mann–Whitney *U*-test. Comparisons of more than two groups were made by analysis of variance (ANOVA). The correlation of NT-pro-BNP with other variables was made using Spearman's coefficient ρ. The area under the receiver operating characteristic (ROC) curve (4) was used to evaluate the utility of elevated NT-pro-BNP, EF by TEE and euroSCORE in predicting post-operative complications after cardiac surgery. Statistical significance was set at $P \leq 0.05$.

Results

For the 135 patients, the mean age was 67 years (range, 56–88 years). The mean (95% CI) serum

NT-pro-BNP level was 1223 ng/l (753–1694 ng/l) and the median (interquartile range, IQR) was 237 ng/l (75–899 ng/l). Normal laboratory values for serum NT-pro-BNP at our institution are less than 230 ng/l for men and less than 330 ng/l for women in patients aged over 50 years. The mean predicted mortality by the logistic euroSCORE was 8.15% (95% CI, 6.20–10.1%). The actual mortality was 5.9% (95% CI, 1.9–9.9%) (Table 1). There was a significant correlation between serum NT-pro-BNP and euroSCORE ($r = 0.658$; $P < 0.001$) and a negative correlation between serum NT-pro-BNP and EF ($r = -0.293$; $P = 0.001$).

The mean BNP level was higher in patients who stayed for more than 2 days in the ICU (705 vs. 3118 ng/l; $P < 0.001$) or died within 28 days of surgery (Table 2). When we examined the 28-day post-operative mortality, there was a significant difference in serum NT-pro-BNP levels between patients who survived for more than 28 days after surgery and those who died within 4 weeks of surgery (1163 vs. 2184 ng/l; $P = 0.001$). The mean serum NT-pro-BNP levels were also higher for those who needed inotropic support and/or IABP for more than 24 h after surgery (548 vs. 2628 ng/l; $P < 0.001$; 935 vs. 3705 ng/l; $P < 0.001$; respectively). The mean serum NT-pro-BNP level was also higher for those who developed acute renal failure after surgery (945 vs. 2857 ng/l; $P < 0.001$). There was no significant difference in the serum NT-pro-BNP levels for patients who did and did not suffer MI after surgery. Female patients had significantly higher serum NT-pro-BNP levels than male patients (Table 2).

Table 1

Patient characteristics and peri- and post-operative parameters.

Pre-operative variables	
Age (mean) (years)	67 (56–88)
Female (%)	24
Male (%)	76
Coronary artery bypass grafting (CABG) (%)	56
Off-pump coronary artery bypass (%)	12
Valve repair (%)	12
CABG and valve repair (%)	20
euroSCORE (mean) (%)*	8.15
N-terminal pro-brain natriuretic peptide (mean) (ng/l)	1223
Post-operative variables	
Mortality <28 days (%)	5.9
Peri-/post-operative myocardial infarction (%)	14.1
Inotropes (%)	33
Intra-aortic balloon pump (%)	10
Renal failure (%)	12
Intensive care unit stay >2 days (%)	22

*Predicted mortality by logistic euroSCORE.

Table 2

Mean (95% confidence interval, CI) and median levels of pre-operative serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP) in groups with and without serious complications.

	BNP level (ng/l) ($n = 135$)		P
	Mean (95% CI)	Median	
Gender			
Male	963 (521–1406)	180	
Female	2026 (693–3360)	506	0.002
Inotropic drug support			
Yes	2628 (1489–3768)	964	
No	548 (186–910)	119	<0.001
IABP support			
Yes	3705 (1281–6130)	1795	
No	935 (516–1356)	208	<0.001
28-day mortality			
Yes	2184 (738–3629)	1420	
No	1163 (672–1654)	210	0.001
Post-operative renal failure			
Yes	2857 (1532–4182)	1728	
No	945 (463–1428)	194	<0.001
Intensive care unit stay			
1–2 days	705 (361–1048)	162	
≥3 days or 28-day mortality	3118 (1481–4757)	1041	<0.001
Post-operative myocardial infarction			
Yes	1171 (646–1696)	231	
No	1542 (581–2503)	545	0.12

Serious complications: more than 2 days in the intensive care unit, mortality at 28 days, post-operative inotropic drug support, intra-aortic balloon pump (IABP) support, renal failure and myocardial infarction. $P < 0.05$ is significant.

When the ROC curves were plotted for serum NT-pro-BNP, euroSCORE and EF to compare their utility in predicting a length of stay of more than 2 days in the ICU and/or 28-day mortality, the areas under the curve (AUC) were 0.328 for EF, 0.814 for euroSCORE and 0.829 for serum NT-pro-BNP (Fig. 1). The sensitivity and specificity for predicting the need for inotropic and/or IABP support and renal failure after surgery were also evaluated (Table 3). The AUC values were 0.378, 0.769 and 0.840 for EF, euroSCORE and serum NT-pro-BNP, respectively, in predicting inotropic support, 0.316, 0.739 and 0.792 for EF, euroSCORE and serum NT-pro-BNP, respectively, in predicting IABP support, and 0.335, 0.776 and 0.857 for EF, euroSCORE and serum NT-pro-BNP, respectively, in predicting post-operative renal failure (Table 4).

Discussion

It is very important to be able to evaluate the risk of cardiac surgery. Firstly, it gives the surgeon and patient a better idea of the surgical risk. When

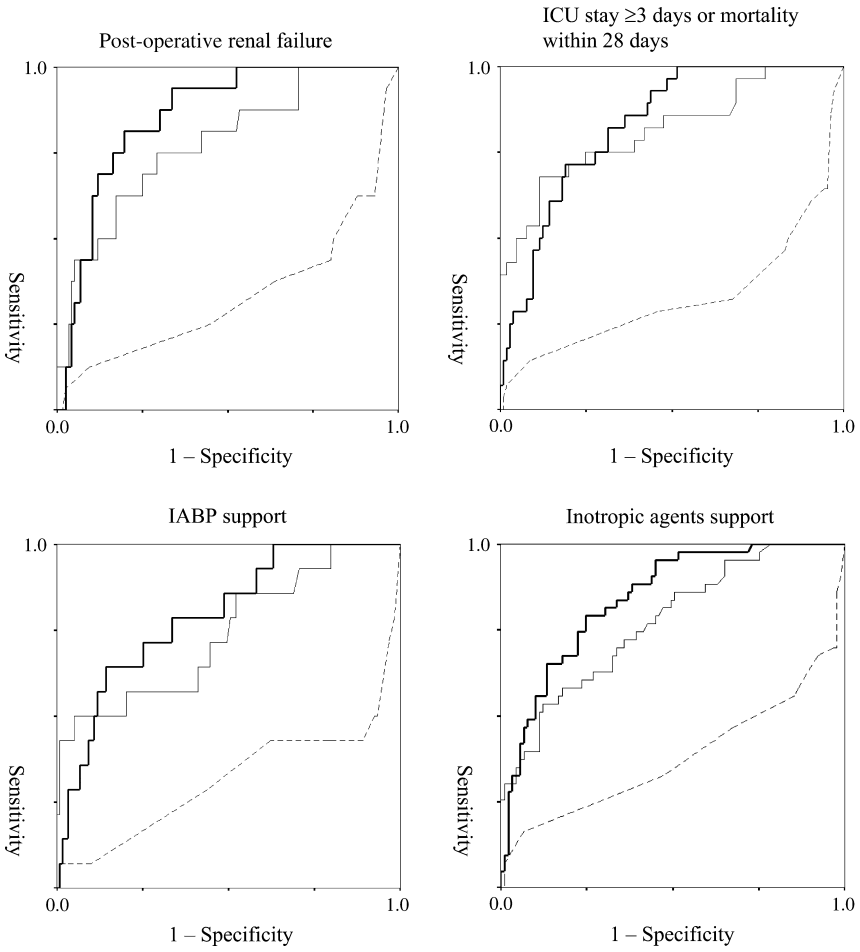

Fig. 1. Receiver operating characteristic (ROC) curves for pre-operative serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP) (bold full line), euroSCORE (full line) and ejection fraction (broken line) evaluated by pre-operative transesophageal echocardiography (TEE) predicting a length of stay in the intensive care unit (ICU) of more than 2 days or death less than 28 days post-operatively, post-operative inotropic or intra-aortic balloon pump (IABP) support or renal failure.

operating on high-risk patients, the surgeon and anesthesiologist are better prepared for perioperative difficulties. It is important for ICU staff to be aware of an increased risk of a prolonged stay in the ICU (>2 days) post-operatively for resource management. Finally, it is important to compare the outcome of surgeries between hospitals and to evaluate the quality of health care.

Our results show that pre-operative NT-pro-BNP is an excellent predictor of post-operative complications after cardiac surgery. The AUC value of NT-pro-BNP is higher than 0.8 in every category. Its utility in predicting complications is better than EF evaluated by TEE before surgery, but after the induction of anesthesia, and as good as the logistic euroSCORE. We defined serious complications as the need to stay for more than 2 days in the ICU, mortality at 28 days, inotropic or IABP support for more than 24 h, post-operative MI or acute renal failure. The majority of patients with no complications only had to stay for 1 day in the ICU. When patients had to stay for more than 2 days in the ICU, complications were the causative factor.

Table 3

N-terminal pro-brain natriuretic peptide (NT-pro-BNP) cut-off values predicting post-operative complications.

	NT-pro-BNP (ng/l)	Sensitivity (%)	Specificity (%)
Inotropes	376	79	75
Intra-aortic balloon pump	396	79	66
Renal failure	404	88	70
Intensive care unit >2 days	376	82	69

Mortality was observed within 28 days in eight patients (5.9%). All of these patients died from congestive heart failure coincident with multiple organ failure, supporting the hypothesis that pre-operative cardiac dysfunction is the predominating risk factor for adverse outcome in cardiac surgery.

Serum NT-pro-BNP predicted whether patients had to stay for 1–2 days in the ICU or for more than 2 days (705 vs. 3118 ng/l; $P < 0.001$). It also predicted mortality at 28 days post-operatively (1163 vs. 2184 ng/l; $P = 0.001$). This is consistent with other

Table 4

Areas under the curve (AUC) and 95% confidence intervals for pre-operative serum N-terminal pro-brain natriuretic peptide (NT-pro-BNP), euroSCORE and ejection fraction (EF) with transesophageal echocardiography (TEE) before surgery, and their utility in predicting whether the length of intensive care unit (ICU) stay will exceed 2 days, the patient will die within 28 days, the need for post-operative inotropic support and intra-aortic balloon pump (IABP) support, and renal failure post-operatively.

AUC	ICU stay $\geq$2 days	Inotropic drug support	IABP support	Post-operative renal failure
Pre-operative serum NT-pro-BNP	0.829 (95% CI, 0.755–0.903)	0.840 (95% CI, 0.772–0.908)	0.792 (95% CI, 0.675–0.910)	0.857 (95% CI, 0.778–0.936)
euroSCORE	0.814 (95% CI, 0.716–0.912	0.769 (95% CI, 0.684–0.908)	0.739 (95% CI, 0.587–0.891)	0.776 (95% CI, 0.653–0.899)
EF	0.328 (95% CI, 0.193–0.463)	0.378 (95% CI, 0.262–0.494)	0.316 (95% CI, 0.131–0.501)	0.335 (95% CI, 0.168–0.501)

recent studies. Cuthbertson et al. (18) found that BNP levels predicted whether a patient had to stay for more than 1 day in the ICU. Kerbaul et al. (19) showed that pre-operative NT-pro-BNP levels were higher for a group of patients with post-operative complications. Complications were defined as the need for inotropic drugs, 30-day mortality, MI, atrial fibrillation, heart failure, ventricular fibrillation and systolic arterial pressure of 90 mmHg or less (19).

In our study, NT-pro-BNP also predicted the need for inotropic drugs and/or IABP for more than 24 h after surgery (548 vs. 2628 ng/l; $P < 0.001$; 935 vs. 3705 ng/l; $P < 0.001$; respectively) and acute renal failure post-operatively (945 vs. 2857 ng/l; $P < 0.001$). We found a negative correlation between NT-pro-BNP levels and EF assessed with TEE before surgery, but after the induction of general anesthesia. Bahar et al. (20) showed that EF $< 50\%$ was a strong risk factor for acute renal failure after cardiac surgery. The difference between the two studies may be the result of the different timing and techniques of evaluation of pre-operative EF.

Our results showed that patients who suffered MI after cardiac surgery did not have significantly higher pre-operative serum NT-pro-BNP levels. MI that occurs after cardiac surgery is often caused by intra-operative complications, and may therefore show little correlation with the pre-operative condition of the heart. Elevated levels of serum NT-pro-BNP correlated significantly with euroSCORE ($r = 0.658$, $P < 0.001$). The study by Cuthbertson et al. (18) also reported this correlation.

The measurement of NT-pro-BNP or BNP may have advantages over euroSCORE and the evaluation of EF as a prognostic indicator. The information needed to calculate euroSCORE is not always available. In our own experience, different physicians may score patients differently. euroSCORE has also been shown to overestimate a patient's risk of death (14, 15). In comparison, NT-pro-BNP is a single test with results that are easily reproduced and corroborated. Like all other blood tests, it must be kept in mind that the measurement of BNP or NT-pro-BNP is dependent on the correct handling of the sample and quality control in the laboratory. It would be interesting to study whether the predictive value of euroSCORE would benefit by adding a measurement of BNP to the algorithm.

EF assessed by TEE by visual estimation is very operator prone, with considerable variability. EF was evaluated by experienced echocardiographers after the induction of general anesthesia. Our results show that the specificity of EF assessed in this way for the prediction of complications after cardiac surgery is poor (AUC = 0.328 vs. 0.829 and 0.814 for serum NT-pro-BNP and euroSCORE, respectively). This contrasts with the study by Bahar et al. (20). A more standardized evaluation of EF, e.g. by measuring the fractional area of shortening (FAS), may be more specific in predicting post-operative complications. The timing of the evaluation and general anesthesia may also have had an impact on the prognostic value of EF in our study. TEE may also be a more sensitive predictor of peri-operative complications if either the left atrial size is measured as an indicator of long-standing left ventricular pressure overload or a thorough diastolic evaluation by Doppler and tissue Doppler is performed. A recent study by Bursi et al. (21) revealed a significant correlation between the levels of BNP and the severity of diastolic function. It seems plausible that diastolic function may be a more sensitive and specific prognostic factor for peri-operative complications, and less operator dependent, than the measurement or evaluation of EF by TEE.

The strengths of this study were the relatively large number of participants ($n = 135$), and the inclusion of a mixed population of patients in a tertiary care facility undergoing various types of cardiac surgery over a period of 12 months: CABG, OPCAB, valve repair and both CABG and valve repair. Both male and female patients were included in this study. Pre- and post-operative data were collected, and euroSCORE

was calculated before the NT-pro-BNP data were collected. The use of AUC values for statistical analysis was also different from similar previous studies.

The following study limitations must be considered. First, NT-pro-BNP was not measured for all patients undergoing cardiac surgery over the 12 months; 179 patients underwent cardiac surgery and serum NT-pro-BNP measurements were made in 135 (75.4%). This is because the measurement of BNP in cardiac surgery patients only recently became a standard in our hospital. Second, a length of stay for more than 2 days in the ICU is only an indication of complications related to cardiac surgery; therefore, other indications, i.e. renal failure and the need for inotropic support, were also used. Third, our hospital records may be incomplete, but we have assumed that this will have only a minimal effect on the quality of the data.

In conclusion, NT-pro-BNP seems to be a significant and valuable prognostic indicator for complications in adult cardiac surgery. This needs to be evaluated further in larger studies and different patient populations.

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