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NT-pro BNP secretion and clinical endpoints in cardiac surgery intensive care patients

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SUMMARY

The primary objective of this study was to determine the pattern of N-Terminal pro brain natriuretic peptide (NT-pro BNP) secretion pre and post cardiac surgery and then to investigate the correlation between levels of serum NT-pro BNP and postoperative clinical and biochemical endpoints. This was a prospective observational study performed at a tertiary centre in New Zealand, examining 118 adult patients undergoing cardiac surgery. Interventions included blood samples for NT-Pro BNP and troponin-T taken 48 hours prior to operation and 12, 36 and 72 hours postoperatively. The plasma NT-pro BNP levels increased fourfold postoperatively, to plateau at 36 to 72 hours. Preoperative NT-pro BNP levels correlated with ventilation time (r=0.46), length of stay in intensive care unit (r=0.59), total perioperative noradrenaline dose (r=0.55), but not with postoperative atrial fibrillation or mortality. Using multivariate analysis, serum NT-pro BNP levels at 36 hours were associated with increased noradrenaline dose (P=0.001), decreased preoperative ejection fraction (EF) Group (P=0.013) and elevated preoperative NT-pro BNP (P<0.001). Factors not associated with NT-pro BNP levels at 36 hours include the operation type, bypass and cross-clamp times, use of milrinone and troponin-T. We conclude that NT-pro BNP levels increased markedly after cardiac surgery and that high preoperative NT-pro BNP levels are associated with a slow postoperative recovery, but do not predict the occurrence of postoperative atrial fibrillation or mortality. Myocardial ischaemia is an unlikely cause of the NT-pro BNP elevation, because no correlation existed between troponin-T and NT-pro BNP levels.

Key Words: brain natriuretic peptide, N-terminal probrain natriuretic peptide, cardiac surgery, intensive care

Brain natriuretic peptide (BNP) and N-Terminal pro brain natriuretic peptide (NT-pro BNP) are useful biochemical markers of left ventricular dysfunction and heart failure. Serum levels of BNP and NT-pro BNP are prognostic in heart failure and myocardial infarction[1,2] and can be used in a diagnostic capacity to determine the presence of heart failure[3,4]. They can also be used to guide treatment of heart failure[5].

Only recently has the role of BNP in the intensive care unit been investigated[6].

The relevance of NT-pro BNP in the setting of cardiac intensive care is, at present, unclear. However, recent evidence from two small studies suggests that plasma concentrations of BNP are elevated after open cardiac surgery and cardioplegic arrest[7,8]. A poorly functioning left ventricle is associated with elevated BNP levels. Furthermore, after cardiac surgery a patient with a poor left ventricle is more likely to require prolonged ventilation[9], and is more likely to require increasing amounts and numbers of inotropic agents. It would also be useful if pre-operative levels of NT-pro BNP could identify the subgroup of cardiac surgery patients who will have a problematic postoperative course (as indicated by increased inotropic requirements, longer ventilation time and longer duration of stay in the intensive care unit).

The objectives of this study were to determine the pattern of secretion of NT-pro BNP after cardiac surgery and correlate the level of NT-pro BNP to clinically significant postoperative endpoints—namely 1) prolonged ventilation time, 2) prolonged intensive care stay, 3) increased inotropic requirements and

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iv) the development of postoperative atrial fibrillation following cardiac surgery. We also undertook multivariate statistical modelling to identify other factors that may influence the perioperative pattern of NT-pro BNP secretion and therefore possibly gain some understanding of the pathophysiological significance and mechanisms underlying NT-pro BNP secretion in this patient group.

MATERIALS AND METHODS

During a six-month period (from July 2003 to December 2003), 118 consecutive adult patients presenting for cardiac surgery were prospectively assessed at Waikato Hospital. Ethical approval was granted from the Waikato Ethics Committee. Inclusion criteria were: all patients undergoing coronary artery bypass grafting (CABG) and/or undergoing valvular surgery and who were able to provide informed written consent. Exclusion criteria were: acute cardiac instability requiring an urgent operation and/or inability to give informed consent. Blood samples for NT-pro BNP levels were taken 48 hours preoperatively and at one, 12, 36 and 72 hours (stored at -70°C) and samples for troponin T (TnT) were taken 48 hours preoperatively and at one, 12 and 36 hours post bypass. Plasma NT-pro BNP and troponin T assays were analysed by Roche Modular E170 Unit (Roche Diagnostics Basel, Switzerland). The investigators were blinded to the blood test results until clinical data collection was complete.

Co-morbidities, patient symptoms and Euroscore[10] information were obtained from the clinical records. The most recently recorded echocardiographic and angiographic studies were used to determine ventricular function prior to the operative procedure. Patients were divided into three groups according to their ejection fraction (EF): EF Group 1 <35%, EF Group 2 35-55% and EF Group 3 >55%.

After premedication with oral lorazepam (2-4 mg), the patients were anaesthetised with etomidate (0.1 mg/kg IV) and fentanyl (25-50 μg/kg IV) and anaesthesia maintained with isoflurane (1%) and propofol (200-300 mg/h IV). Pancuronium 8-12 mg IV was used to obtain muscle relaxation. Cephazolin 1 g was given for antibiotic prophylaxis. The patient's trachea was then intubated and a nasal temperature probe, right internal jugular central line and indwelling bladder catheter inserted. A pulmonary artery catheter was floated if there was evidence of poor left ventricular function, complex valve lesions, predicted long cardiopulmonary bypass, or any other situation where knowledge of cardiac output was thought to be required. Heparin (350 units/kg) was used for bypass anticoagulation, the heart was infused with cardioplegia solution (composition dependent on surgeon's preference) and the patient then placed onto cardiopulmonary bypass. Transoesophageal echocardiography was used routinely during each operation (Hewlett Packard 2500 with a Phillips probe). Temperature was maintained at 32°C and the patient rewarmed to 36.4°C at the conclusion of surgery.

Coming off bypass, noradrenaline and milrinone were used at the discretion of the anaesthetist. The primary indications were hypotension despite adequate volume loading, poor LV function and moderate or severe diastolic dysfunction as seen on transoesophageal echo. Protamine (10 mg IV/1000 IU of heparin) was administered at the end of cardiopulmonary bypass. Patients were subsequently transferred to the cardiac intensive care unit and ventilated using SIMV volume control/pressure support modes while propofol and inotropic infusions were continued. Inotrope and vasoconstrictor drugs were infused to maintain target values of mean arterial blood pressure (70-90 mmHg) and cardiac indices (>2.2 l/min/m^2), while simultaneously treating low preload with intravenous fluids as required. Extubation was considered when the patient was awake, alert and haemodynamically stable without ongoing bleeding and with an arterial oxygen partial pressure >80 mmHg when breathing an inspired oxygen of <50%. Intraoperative complications were identified from intensive care data entry and surgical notes. Ventilation time, inotropic use and the presence of atrial fibrillation were determined from intensive care 24-hour assessment sheets. While the patient was in intensive care, nurses identified periods of arrhythmia on the data sheets and the investigation team reviewed the appropriate telemetry sequence. The patient was considered to have postoperative atrial fibrillation if the arrhythmia persisted for longer than 30 seconds (provided there was no previous history of chronic atrial fibrillation). Other postoperative outcomes documented included reintubation, tracheostomy, excessive blood loss and duration in intensive care. Survival at six months was ascertained by contacting the primary medical practitioner.

STATISTICAL ANALYSIS

Univariate analysis

Unless otherwise stated, data are presented as mean (SD). The NT-pro BNP concentrations were logarithmically transformed (and the noradrenaline dosages were square-root transformed to avoid the logarithm of zero) to obtain a Gaussian

distribution (Kolmogorov-Smirnov test). The strength of association between continuous variables was quantified using the Pearson correlation coefficient (r). The within-subject changes of NT-pro BNP level with time were modelled using repeated-measures ANOVA. We used the Bonferroni correction for post hoc multiple comparisons. We used the 36-hour postoperative NT-pro BNP as a primary indicator of the magnitude of the post-operative NT-pro BNP response. The requirement to stay in ICU longer than 24 hours was used as a composite binary endpoint, indicative of a complicated postoperative course. We used the area under the receiver operating characteristic (ROC) curve as a measure of various predictors of this binary endpoint.

Multivariate analysis

In order to develop an explanatory multivariate model of the postoperative increase in NT-pro BNP, we used a backward stepwise elimination general linear model (P=0.15 to remove a term). Initial factors in this model included age, gender, creatinine, preoperative EF Group, preoperative NT-pro BNP, troponin-T, operation type, cross-clamp time, bypass time, noradrenaline dose, milrinone and interaction terms. To determine the ability of various pre- and intraoperative variables to classify the patients into groups—e.g. those needing noradrenaline, or milrinone, or who subsequently developed atrial fibrillation—we used a linear discriminant function (LDF). All statistical calculations were done using the SYSTAT computer program (SYSTAT version 10, SPSS Inc, Chicago, IL, U.S.A.).

RESULTS

Baseline characteristics of the patients are set out in Tables 1 and 2. Ninety-one patients underwent coronary artery bypass grafting. A total of 25 patients underwent a valve operation. Of these, 10 had combination procedures; that is a valve replacement in conjunction with another procedure, predominantly CABG. Two patients had 'other' procedures. One underwent resection of a symptomatic atrial myxoma and the second underwent a Bentall's procedure for dilatation of the ascending aorta. Fifty-four percent of patients required noradrenaline support (n=64). Patients were grouped heuristically according to their postoperative noradrenaline requirements: 1) 'No-NA' (0 μg/min, n=54), 2) 'Low-NA' (0-7 μg/min, n=50) and 3) 'High-NA' (>7 μg/min, n=14). Nineteen patients were given milrinone intraoperatively and 16 required milrinone postoperatively. No patient returned to theatre. Two perioperative deaths were identified, one patient from multi-organ failure 48 hours postoperatively in the intensive care unit, whilst the second died as a result of a cerebrovascular accident on day 9 postoperatively. There were no further deaths at six-month follow up.

TABLE 1
Operations performed

Operation numbers	
CABG	91 (77.1%)
AVR only	7 (5.9%)
MVR only	8 (6.8%)
Combination	10 (8.5%)
Total AVR	15 (12.7%)
Total MVR	10 (8.5%)
Other	2 (1.7%)
Total	118

CABG—coronary artery bypass grafting.
AVR—aortic valve replacement.
MVR—mitral valve replacement.

TABLE 2
Patient characteristics (mean (SD) or numbers (%))

Age (y)	64 (9)
Gender (male)	84 (71%)
Hypertension	66 (56%)
Diabetes	19 (16%)
Preoperative atrial fibrillation	13 (11%)
EF<35%	13 (11%)
EF 35-55%	25 (21.1%)
EF>55%	80 (67.8%)
NYHA I	2 (1.7%)
NYHA II	28 (23.7%)
NYHA III	65 (55%)
NYHA IV	25 (21.2%)
Bypass time (min)	119 (53)
Cross clamp time (min)	80 (43)
ICU stay (hours)	27 (18)
Ventilation time (hours)	11 (13)
Postoperative stay (days)	8.5 (3.1)

NYHA—New York Heart Association.
EF—ejection fraction.

TABLE 3
Perioperative changes in plasma NT-pro BNP and Troponin-T concentrations for each of the different operations (mean (SD), pmol/l and ug/l respectively)

Operation type	CAVG	AVR	MVR	Combo
NT-pro BNP				
Preoperative	100(17)	584(305)	245(94)	1057(796)
12 hours	270(144)	366(201)	322(170)	722(714)
36 hours	514(206)	927(713)	726(422)	1299(1215)
72 hours	626(304)	397(103)	987(511)	1603(1192)
Troponin T				
Preoperative	0.15(0.23)	0.01(0.00)	0.01(0.00)	0.02(0.01)
12 hours	0.40(0.22)	0.37(0.12)	0.74(0.50)	0.38(0.20)
36 hours	0.37(0.21)	0.31(0.09)	0.38(0.13)	0.65(0.32)

Secretion pattern of NT-pro BNP

NT-pro BNP levels increased following cardiac surgery from preoperative baseline levels differently for the different surgical categories (Table 3). The NT-pro BNP level was related to the ejection fraction grading. EF Group 1 had significantly higher NT-pro BNP levels than found in those with EF Group 2 and EF Group 3 ($P<0.01$). The NT-pro BNP levels increased about fourfold postoperatively in all groups (see Figures 1 and 2) plateauing at 36 to 72 hours. The multivariate model (backward stepwise elimination general linear model) revealed 1) noradrenaline dose ($P=0.001$), 2) preoperative EF Group ($P=0.013$) and 3) preoperative NT-pro BNP ($P<0.001$) as significant independent factors in explaining the 36-hour NT-pro BNP level (adjusted $R^2=0.54$). The operation type, bypass and cross-clamp times, use of milrinone, troponin-T and interaction terms were not found to be significant independent explanatory variables in this model.

NT-pro BNP levels and clinical endpoints

Preoperative NT-pro BNP levels were significantly positively correlated with 1) ventilation time (r=0.46, $P=0.015$), 2) length of stay in ICU (r=0.59, $P=0.001$) and 3) total perioperative noradrenaline dose (r=0.55, $P=0.003$). Preoperative NT-pro BNP levels also correlated with age (r=0.42, $P=0.01$), creatinine (r=0.43, $P=0.01$), EuroSCORE (r=0.54, $P=0.003$) and bypass time (r=0.49, $P=0.08$). There were no significant correlations with gender, or between preoperative NT-pro BNP and medication (including beta blockers or IV heparin) and NYHA class. The preoperative NT-pro BNP level produced a similar area under the ROC curve to that derived from the EuroSCORE (0.66 vs. 0.68) in predicting the chance of prolonged ICU length of stay

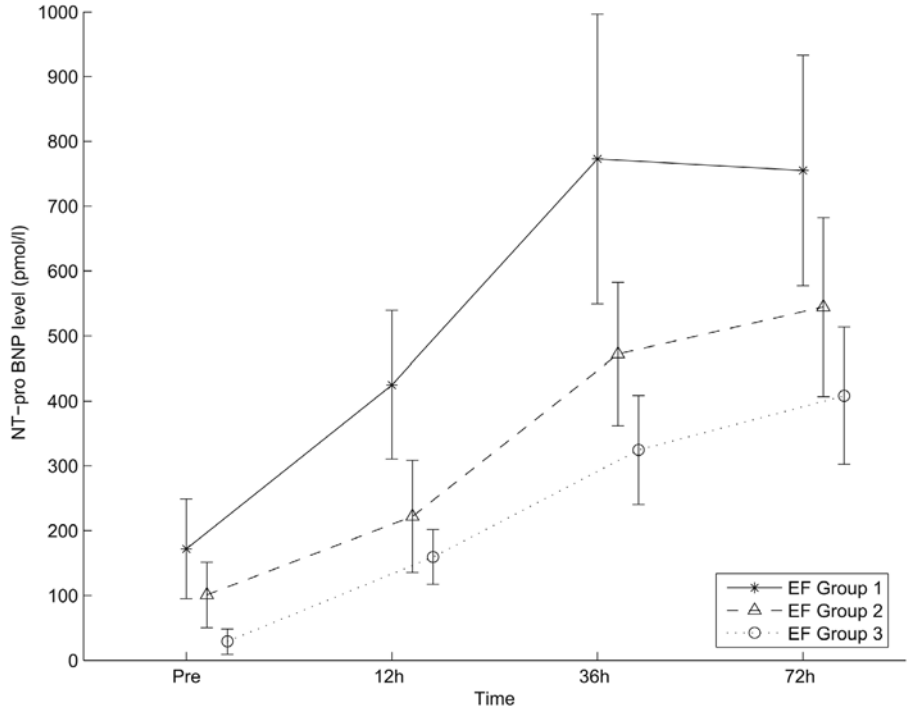

FIGURE 1: Perioperative changes (median, interquartile range) in NT-pro BNP for different ejection fraction (EF) groups. The NT-pro BNP was not logarithmically transformed for the purposes of graphic display.

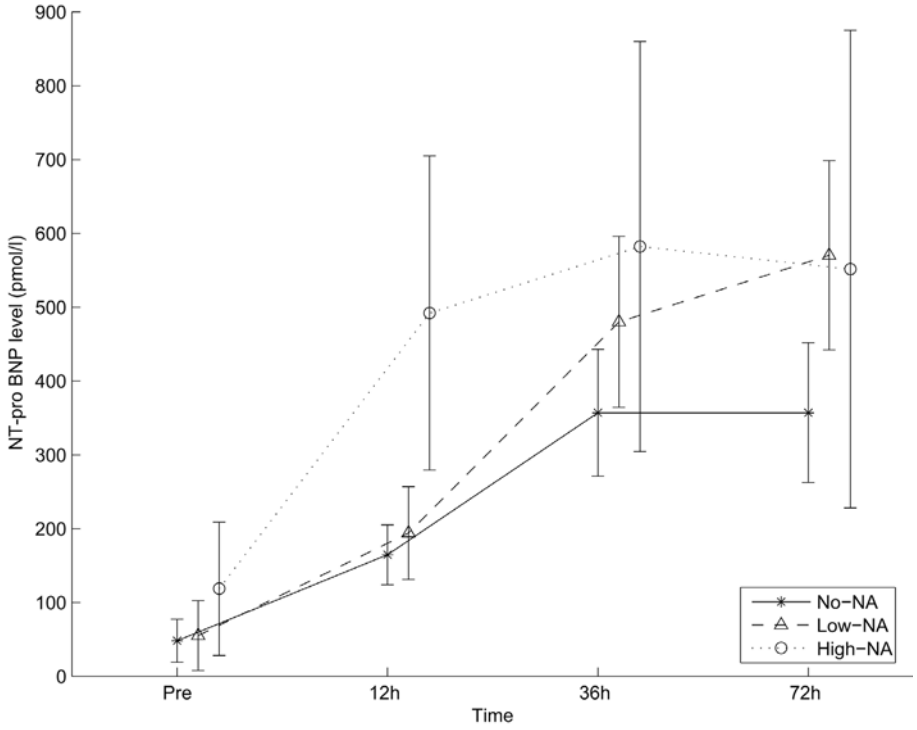

FIGURE 2: Perioperative changes (median, interquartile range) in NT-pro BNP for different noradrenaline groups ('No-NA' (0 μg/min), group 'Low-NA' (0.1-7 μg/min) and group 'High-NA' (>7 μg/min).

(>24 hours). Combination of the two predictors in a logistic regression model did not significantly improve the relatively modest ROC area (area=0.71). This ROC area corresponds to an error of classification of about 30%.

Although there was a statistically significant association between preoperative NT-pro BNP levels and the need for noradrenaline postoperatively (No-NA vs. High-NA, P=0.01, t-test), it was not strong enough to be a useful predictor. Using a linear discriminant function, the error in classification was almost 50% and the Wilks' lambda, P=0.29. The subgroup of patients who went on to require milrinone (n=16) had higher preoperative mean (SD) NT-pro BNP levels (860(502) pmol/l, vs. 122(23) pmol/l, P=0.004, t-test on logarithmically transformed data).

Atrial fibrillation

The patients who were in atrial fibrillation preoperatively (n=11) had significantly higher NT-pro BNP levels (301 (82) pmol/l) than those who were in sinus rhythm (225 (87) pmol/l, P=0.01, t-test). However there was no significant difference in NT-pro BNP levels in those patients who subsequently developed atrial fibrillation at any time postoperatively. The factors that were found to be significant in a forward stepwise LDF to classify the development of postoperative atrial fibrillation were: 1) ejection fraction group and 2) preoperative troponin-T level (69% correct classification).

Troponin-T levels

Troponin-T levels increased significantly postoperatively (Table 3) and relatively more markedly in those patients with: 1) worse left ventricular function (EF Groups 2 and 3 (P<0.001, repeated-measures ANOVA)) and 2) in the High-NA group (P=0.005, ANOVA). Preoperative troponin-T levels did not correlate significantly with ventilation time, length of stay in ICU, noradrenaline requirements, EuroSCORE, or EF group. The 12-hour postoperative troponin-T levels did correlate weakly, but significantly, with length of ventilation (r=0.39) and length of ICU stay (r=0.29). The 36-hour troponin-T levels correlated significantly with cross-clamp time only for the CABG patients (r=0.36, P=0.002). There were no significant correlations between troponin-T levels and NT-pro BNP levels at any time point; or within the valve surgery or CABG patient subgroups.

DISCUSSION

The role of NT-pro BNP in intensive care is unclear at present. There have been a number of other recently published studies determining the

relationship between BNP, N-Terminal BNP and endpoints after cardiac surgery[11-15]. Our study showed that NT-pro BNP significantly increased after cardiac surgery, reaching peak levels at 36 to 72 hours. Using multivariate analysis, the main factors explaining this increase were found to be: 1) the preoperative NT-pro BNP level, 2) the ejection-fraction class and 3) early postoperative noradrenaline requirements. We also found statistically significant correlations between preoperative NT-pro BNP and duration of ventilation, inotropic requirements and duration of intensive care stay postoperatively, but these were not strong enough to be clinically useful predictors on their own. We found no correlation between NT-pro BNP levels and troponin-T levels, or the propensity to develop atrial fibrillation.

McLean and co-workers were first to explore the role of BNP in the general intensive care unit. They found that patients with cardiac dysfunction, as determined by echocardiography, had higher BNP levels than those without cardiac dysfunction[6] and they concluded that BNP could be used to screen for cardiac dysfunction. Two smaller studies that looked at BNP changes after cardiac surgery (both CABG and valve surgery) have been published subsequent to our data collection[11,14]. The study by Hutfless et al[14] differed from ours because they only studied males and >10% of their patients had intra-aortic balloon pumps. They were able to find significant correlations between preoperative BNP and certain postoperative endpoints, including use of intra-aortic balloon pumps, death at one year and prolonged hospital stay. Berendes et al[11] focussed primarily on secretion patterns of BNP after cardiac surgery. They found a slightly different time course of BNP (not NT-pro BNP) secretion, with maximum levels earlier (24 hours postoperatively) than we found in our study. We found that NT-pro BNP increased to differing levels dependent on the type of surgical procedure. The increase was correlated with cross-clamp time only in the CABG group. This pattern of secretion was consistent with Berendes' study[11].

Pathophysiological mechanisms that cause the increase in NT-pro BNP levels are not clear. Georges et al[13] assessed the secretion pattern of BNP in a small group of patients (n=35) and hypothesised that cardiac ischaemia, associated with stunned myocardium, was the likely stimulus for BNP secretion. This was thought to be secondary to aortic cross-clamping and cardioplegic arrest after instituting cardiopulmonary bypass, with resulting decreased myocardial contractility and increased filling pressures. We think that this explanation is unlikely for the following reasons: 1) NT-pro BNP has a relatively short elimination half-life of (~90 minutes) and the maximal elevation in plasma levels occurred 36 to 72 hours after the bypass; 2) there was no correlation between troponin-T levels and NT-pro BNP levels. In contrast, the multivariate statistical modelling of the postoperative NT-pro BNP elevation suggested that pre-existing myocardial dysfunction (as estimated by preoperative NT-pro BNP levels and ejection fraction group) was more important than intraoperative factors. Our data (which show a delayed increase) do support the conventional idea that NT-pro BNP levels are related to increased intracardiac pressure or myocardial stretch before the operation. It is easy to envisage that the stretch will get proportionately worse with the stress of the operation, particularly in the later phases of the recovery period (24 to 96 hours) when the body is in a fluid-retaining state. The cause and effect relationship between NT-pro BNP and noradrenaline dosage is unclear from our study design. Noradrenaline will often be required for cardiovascular support in the group of patients with intrinsically poor myocardial function. Whether NT-pro BNP is a direct mediator of post-surgery vasoplegia is at present unknown.

We also speculated that preoperative or post-operative NT-pro BNP would correlate with new onset atrial fibrillation in the postoperative period. In contrast to a study by Wazni et al[15], we found no association of new atrial fibrillation either with NT-pro BNP or troponin T.

We conclude that NT-pro BNP levels increase progressively (~fourfold) over the first few days postoperatively. This increase is correlated with pre-existing NT-pro BNP levels, ejection fraction and noradrenaline requirements. Preoperative NT-pro BNP levels (but not preoperative troponin-T levels) correlate with a slow postoperative recovery but do not predict the occurrence of postoperative atrial fibrillation or mortality.

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