Preoperative Brain Natriuretic Peptide Predicts Late Mortality and Functional Class but Not Hospital Readmission After Cardiac Surgery

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Objectives: **N-terminal brain natriuretic peptide (NT-proBNP) is an established biomarker of heart failure and has been found to predict mortality and morbidity after cardiac surgery. The aim of this study was to investigate whether preoperative NT-proBNP can predict postoperative New York Heart Association (NYHA) functional class and hospital readmission in addition to morbidity and mortality.**

Design: **Retrospective.**

Setting: **University hospital.**

Participants: **All patients undergoing aortic valve replacement for aortic stenosis and coronary artery bypass grafting from January to December 2008 (n = 390).**

Measurements and Main Results: **Preoperative NT-proBNP was recorded prospectively. Five-year mortality was obtained through national registries. Postoperative functional class, morbidity, and hospital readmission were obtained through telephone interviews. Patients were divided into quartiles based on preoperative NT-proBNP; the medians of each quartile were 103 ng/L, 291 ng/L, 825 ng/L and 2,375 ng/L. Increased preoperative NT-proBNP was associated with reduced postoperative functional class. In the first quartile, 7% (7/97) were in NYHA functional class III-IV compared to 26% (25/97) in the fourth quartile ($p < 0.01$). Increased preoperative NT-proBNP was also associated with reduced long-term survival ($p < 0.01$). The covariate adjusted hazard ratio for mortality in the fourth quartile was 2.9 (1.61-5.08; $p < 0.01$) compared to the other quartiles. No association was found between preoperative NT-proBNP and postoperative hospital readmission.**

Conclusions: **Increased preoperative NT-proBNP is associated with reduced long-term survival and functional class but not hospital readmission post-cardiac surgery. Thus, NT-proBNP might have additive value to established risk factors in the preoperative assessment of patients undergoing cardiac surgery.**

KEY WORDS: cardiac surgery, heart failure, mortality, morbidity, postoperative outcome, B-type natriuretic peptide

THE VALUE of both brain natriuretic peptide (BNP) and its N-terminal portion (NT-proBNP) as prognostic and diagnostic biomarkers has been studied extensively in patients with heart failure and acute coronary syndrome and, more recently, also in patients undergoing cardiac surgery.[1–3] In cardiac surgery, both markers have been found to predict short-term and long-term mortality as well as symptom-free survival.[4–8]

Several attempts have been made to further clarify the role of NT-proBNP, both as a sole predictor but also its additive value to established risk factors such as reduced left ventricular (LV) function in cardiac surgery patients. Preoperative BNP and NT-proBNP also have been shown to predict postoperative complications such as atrial fibrillation (AF), heart failure, need for inotropic drugs, renal failure, and prolonged hospital stay in patients undergoing both coronary artery bypass grafting (CABG) and aortic valve replacement (AVR).[4,6,7,9,10] Thus, there already is support for the use of preoperative BNP/NT-proBNP as a marker for an adverse outcome after cardiac surgery procedures.

To further investigate the relation of this biomarker to timing of cardiac surgery, more recent studies have searched for preoperative cut-off levels that could indicate increased postoperative morbidity and mortality.[3,7,8] However, to advocate earlier surgery in patients with increased NT-proBNP, preoperative levels must be associated with increased mortality as well as an adverse outcome in terms of postoperative function for the patient.

To the authors' knowledge, no study has focused on the utility of NT-proBNP in predicting postoperative functional class and morbidity, more specifically hospital readmission. Both reduced functional class and hospital readmission might reflect surgical correction too late in the disease process and morbidity related to the surgical procedure. Even though the patients survive the surgical procedure, the burden of morbidity can shadow the long-term result in terms of reduced physical capacity and quality of life.

In this study, the authors hypothesized that increased preoperative NT-proBNP could predict long-term mortality, reduced functional class, and hospital readmission after cardiac surgery.

METHODS

All patients (n = 390) undergoing CABG (n = 234), isolated AVR (n = 114) for aortic stenosis (AS) and isolated AVR for AS with concomitant CABG (n = 42) from January 1, 2008 through December 31, 2008 were included in this study. Exclusion criteria were significant aortic insufficiency and double-valve procedures. The study was performed after approval by the local human ethics committee. All patients were informed and agreed to participate in the followup of clinical variables that were entered into the analyses. All procedures were performed with standard technique on extracorporeal circulation (ECC).

Clinical data were recorded prospectively. The following variables were entered into the database preoperatively: Age, sex, left ventricular (LV) function, New York Heart Association (NYHA) functional class, rhythm, hypertension, diabetes, positive inotropic medications, preoperative stroke, hemoglobin, and creatinine. Operative variables were recorded postoperatively: ECC-time, intra-aortic balloon pump (IABP), ventricular assist device (VAD), positive inotropic medications, postoperative rhythm, dialysis, blood transfusion, intensive care unit (ICU) stay, hospital stay, postoperative stroke, infections, and early mortality (ie, 30-days mortality).

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Plasma NT-proBNP was sampled 1 day preoperatively in addition to routine blood analysis, and values were available for all patients. The blood samples were analyzed at the laboratory for clinical biochemistry by immunoassay using a Modular Analytics E170 (Roche Diagnostics, Indianapolis, IN).

Patient followup regarding NYHA functional class, postoperative stroke, anticoagulation, postoperative rhythm, hemorrhage, and hospital readmission was carried out through telephone interviews with the patients. Hospital readmission was defined as admission to the hospital due to any cause. The time to readmission after surgery was divided into less than 1 month, 1-3 months, 3-6 months, or more than 6 months. The number of admissions was classified into 1 time, 2-5 times, or more than 5 times. If patients had been readmitted to the hospital, hospital discharge data were obtained to verify diagnosis. The median followup for telephone interviews was 32 months, with a response rate of 90%.

Survival data were obtained through a continuously updated population register; thus, all patients could be assigned a date of death or identified as being alive. The followup was performed on July 1, 2013, with a median followup of 60 months (ie, 5 years) since surgery.

Statistical analysis was performed in SPSS version 20.0 (SPPS Inc. Chicago, IL). Patients were divided into quartiles based on preoperative NT-proBNP value for analysis and comparison. Categoric variables were expressed as percentages and continuous variables as mean ± standard deviation. Categoric variables were compared using X^2-test and continuous variables using analysis of variance (ANOVA). P-values < 0.05 were considered statistically significant.

Kaplan-Meier plots for each quartile were used for survival analysis; comparison of significant differences in survival among the quartiles was done with a log-rank test (Mantel-Cox). Stepwise Cox proportional hazard analysis was used for risk adjustment and to identify independent preoperative risk factors for overall mortality. The inclusion limit for stepwise backward elimination was a p value < 0.05. The following variables were included in the analysis: Age, sex, diabetes, hypertension, LV ejection fraction, hemoglobin, creatinine, and NT-proBNP. Among these variables, age, hemoglobin, creatinine, and NT-proBNP were found to be significant predictors.

A receiver operator characteristics (ROC) curve also was plotted to identify sensitivity and specificity for NT-proBNP values to predict mortality.

RESULTS

All patients were divided into quartiles based on preoperative NT-proBNP values. The median value of NT-proBNP in the quartiles were: 103 ng/L, 291 ng/L, 825 ng/L and 2,375 ng/L (Table 1).

Increased preoperative NT-proBNP was associated with older age, female sex, reduced LV function, diabetes, preoperative AF, need for preoperative inotropic support, IABP, low hemoglobin concentration and increased creatinine (Table 1). There was also

Table 1. Patient Characteristics Divided by Preoperative NT-proBNP-Quartile, n = 390

Variable*	First Quartile (n = 97)	Second Quartile (n = 98)	Third Quartile (n = 98)	Fourth Quartile (n = 97)	p Value
NT-proBNP, ng/L (Median)	103	291	825	2375	
NT-proBNP, ng/L, (IQR)	60 - 140	238 - 379	598 - 1055	1770 - 4360	
NT-proBNP, ng/L (Range)	5 - 195	196 - 470	486 - 1325	1326 - 45931	
Diagnosis					<0.01
CABG	76 (78)	70 (71)	47 (48)	41 (42)	
AVR	16 (17)	26 (27)	34 (35)	38 (39)	
AVR + CABG	5 (5)	2 (2)	17 (17)	18 (19)	
Age, mean (SD), years	63 (9)	68 (9)	71 (9)	73 (9)	<0.01
Sex					0.01
Male	85 (88)	70 (71)	67 (68)	69 (71)	
Female	12 (12)	28 (29)	31 (32)	28 (29)	
LVEF					<0.01
≥50%	94 (97)	87 (89)	75 (77)	46 (47)	
30-50%	2 (2)	10 (10)	19 (19)	32 (33)	
<30%	1 (1)	1 (1)	4 (4)	19 (20)	
Rhythm					<0.01
Sinus/PM	92 (95)	92 (94)	84 (86)	74 (76)	
AF	5 (5)	6 (6)	14 (14)	23 (24)	
NYHA-class					0.33
I	4 (4)	2 (2)	1 (1)	1 (1)	
II	18 (19)	12 (12)	18 (18)	11 (11)	
III	73 (75)	81 (83)	73 (75)	76 (78)	
IV	2 (2)	3 (3)	6 (6)	9 (9)	
Hypertension	88 (91)	89 (91)	86 (88)	91 (94)	0.55
Diabetes	18 (19)	23 (24)	16 (16)	33 (34)	0.02
Inotropes/IABP	0 (0)	0 (0)	0 (0)	4 (4)	0.01
CVL					0.21
Stroke	6 (6)	3 (3)	5 (5)	12 (12)	
TIA	2 (2)	3 (3)	2 (2)	1 (1)	
Hemoglobin, mean (SD), g/L	148 (12)	139 (14)	139 (12)	136 (16)	<0.01
Creatinine, mean (SD), mmol/L	79 (15)	80 (21)	82 (25)	93 (42)	<0.01

NOTE: The p values represent comparison among quartiles 1-4.

Abbreviations: AF, atrial fibrillation; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CVL, cerebral vascular lesion; IABP, intra-aortic balloon pump; IQR, interquartile range; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal brain natriuretic peptide; NYHA, New York Heart Association; PM, pacemaker; SD, standard deviation; TIA, transient ischemic attack.

*Values are presented as number and percentage of patients unless specified otherwise.