N-Terminal Pro–Brain Natriuretic Peptide and Outcomes in Patients Undergoing Surgical Ventricular Restoration

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N-terminal pro–brain natriuretic peptide (NT–pro-BNP) levels have been shown to be increased at baseline in patients undergoing surgical ventricular restoration (SVR) of the left ventricle. However, changes in the values of this marker in the early postoperative period and its prognostic significance remain less known in these patients. We evaluated 31 consecutive patients undergoing SVR who had NT–pro-BNP determined a day before SVR and from postoperative days 0 to 4. Major morbidity was defined as ≥1 of the following: ventilation >48 hours, stroke, acute renal failure, low cardiac output, reoperation, or mediastinitis. The association of preoperative NT–pro-BNP with perioperative outcomes was assessed using multivariable logistic regression analysis. Receiver operating characteristic curve was used to test its discrimination power. Major morbidity occurred in 16 patients (52%) with only 1 death within 30 days of SVR. Mean preoperative NT–pro-BNP was 4.5-fold higher in patients with postoperative major morbidity than in those without it (3,022 ± 2,981 vs 676 ± 533 pg/ml, p = 0.007). On multivariate analysis, preoperative NT–pro-BNP was independently associated with major morbidity after adjusting for baseline confounding, particularly age, ejection fraction, and European System for Cardiac Operative Risk Evaluation (odds ratio 1.002, 95% confidence interval 1.001 to 1.003, p = 0.032). Preoperative NT–pro-BNP had a high discrimination power on receiver operating characteristic analysis for major morbidity (area under the curve 0.84, sensitivity 68%, and specificity 88% for 1,304 pg/ml). Although NT–pro-BNP levels decreased after SVR in patients without major morbidity, their levels remained persistently increased in those with it. In conclusion, preoperative NT–pro-BNP determination may be of value in stratifying the risk for major morbidity after SVR. **(Am J Cardiol 2010;105:640–644)**

In small cohort of patients undergoing surgical ventricular restoration (SVR), plasma N-terminal pro–brain natriuretic peptide (NT–pro-BNP) and/or BNP have been shown to be increased at baseline.[1–3] Furthermore, after SVR these levels decreased and this decrease paralleled improvement in left ventricular function and symptoms.[1–3] However, these studies did not evaluate the prognostic significance of baseline NT–pro-BNP on immediate or long-term outcomes. Furthermore, BNP levels were collected at baseline and then 3 to 6 months after surgery, precluding insight into what happens to BNP levels during index hospitalization and the implication of change in these levels on in-hospital outcomes. As such, the immediate postoperative course of NT–pro-BNP and the association of preoperative NT–pro-BNP with perioperative outcomes in patients undergoing SVR are not known. Accordingly, the goal of the present study was to evaluate changes in perioperative NT–pro-BNP in patients undergoing SVR over time during their index hospitalization and to assess the association of preoperative NT–pro-BNP with in-hospital outcomes in patients undergoing this procedure. We hypothesized that SVR results in significant immediate decrease in postoperative NT–pro-BNP over time and that preoperative NT–pro-BNP and changes in its value postoperatively are associated with morbidity and mortality in patients undergoing SVR.

Methods

We evaluated retrospectively consecutive patients who underwent elective SVR with coronary artery bypass graft (CABG) at our institution from January 2007 to December 2008. Of 45 patients undergoing SVR during this period, preoperative value of NT–pro-BNP was not available in 14 patients, excluding them from analysis. The remaining 31 patients formed the basis of the study. These patients had a complete NT–pro-BNP assessment including the preoperative value and values at arrival in the intensive care unit (ICU; day 0) and daily measurements until postoperative day 4. The local ethics committee waived the need for approval of the study. All patients in the study gave in-

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Table 1
Demographics, co-morbidity, and operations details in the overall population and for the two groups

Variable	Overall (n = 31)	Preoperative NT–pro-BNP		p Value
		>1,304 pg/ml (n = 13)	≤1,304 pg/ml (n = 18)	
Age (years)	62 (56–71)	67 (56–75)	60 (56–67)	0.096
Ejection fraction	0.35 (0.29–0.39)	0.33 (0.26–0.36)	0.37 (0.33–0.42)	0.044
Body surface area (m^2)	1.90 (1.81–2.0)	1.81 (1.7–2.0)	2.0 (1.8–2.1)	0.065
Hemoglobin (mg/dl)	14 (13–15)	13 (12–14)	14 (13–15)	0.051
Serum creatinine (mg/dl)	1.1 (0.98–1.3)	1.1 (0.99–1.7)	1.1 (0.92–1.25)	0.559
Creatinine clearance (ml/min)	73 (48–95)	67 (41–81)	81 (56–99)	0.316
Women	2 (6.5%)	2 (15%)	0 (0%)	0.085
New York Heart Association class III–IV	18 (58%)	9 (69%)	9 (50%)	0.282
Previous myocardial infarction	30 (97%)	13 (100%)	17 (94%)	0.989
Family history of cardiovascular disease	14 (45%)	5 (38%)	9 (50%)	0.431
Hypertension	16 (52%)	7 (54%)	9 (50%)	0.961
Hypercholesterolemia	15 (48%)	6 (46%)	9 (50%)	0.713
Diabetes	7 (23%)	2 (15%)	5 (28%)	0.368
Previous cerebrovascular accident	6 (19%)	3 (23%)	3 (17%)	0.713
Atrial arrhythmias	5 (16%)	3 (23%)	2 (11%)	0.410
Ventricular arrhythmias	2 (6.5%)	0 (0%)	2 (11%)	0.085
European System for Cardiac Operative Risk Evaluation	6 (5–10)	8 (7–10)	5 (4–6)	0.005
Associated valve procedure	9 (29%)	6 (46%)	3 (17%)	0.074

Values are medians (interquartile ranges) or numbers of patients (percentages).

Table 2
In-hospital outcomes in the overall population and for the two groups

Variable	Overall (n = 31)	Preoperative NT–pro-BNP		p Value
		>1,304 pg/ml (n = 13)	≤1,304 pg/ml (n = 18)	
Mechanical ventilation (hours)	19.5 (13.5–35)	18 (12–21)	18 (12–22)	0.013
Intensive care unit stay (days)	4.5 (3–6)	4 (3–4)	4 (2.5–4.5)	0.003
Blood loss (ml/12 hours)	532 (387–831)	500 (400–675)	500 (375–687)	0.367
Packed red blood cell transfusions (units)	4 (2–5)	3 (2–4)	3 (2–4)	0.272
Peak creatinine (mg/dl)	1.65 (1.2–2.5)	1.5 (1.2–1.7)	1.5 (1.1–1.8)	0.019
Creatinine clearance (ml/min)	60 (28–70)	28 (22–60)	68 (50–72)	0.005
Low cardiac output	12 (39%)	8 (62%)	4 (22%)	0.027
Intra-aortic balloon pump	7 (23%)	5 (38%)	2 (11%)	0.072
Ventricular arrhythmias	1 (3%)	1 (8%)	0 (0%)	0.232
Respiratory failure	3 (10%)	2 (15%)	1 (6%)	0.361
Stroke/coma	1 (3%)	0 (0%)	1 (6%)	0.388
Acute renal failure	7 (23%)	5 (38%)	2 (11%)	0.072
Sepsis	1 (3%)	1 (8%)	0 (0%)	0.232
Surgical reexploration	1 (3%)	1 (8%)	0 (0%)	0.232
Major morbidity	15 (48%)	11 (85%)	4 (22%)	0.001
Mortality	1 (3%)	1 (8%)	0 (0%)	0.232

Values are medians (interquartile ranges) or numbers of patients (percentages).

formed consent for the scientific analysis of their clinical data in an anonymous form.

Clinical information was obtained from our institutional database that routinely collects clinical information on all patients undergoing cardiac surgery at our institution. Preoperative data collection included demographics and co-morbidities, operative details, and perioperative outcomes. For each co-morbid condition, definitions of the European System for Cardiac Operative Risk Evaluation (EuroSCORE) were followed.[4] Risk stratification was performed using the additive EuroSCORE. Intraoperative data included type of operation performed (SVR + CABG or SVR + CABG + valvular procedure). Postoperative outcome data included major morbidity according to the Society of Thoracic Surgeons definition[5] (any of the following: need for reoperation, sternal wound infection, permanent stroke, renal failure, mechanical ventilation for >48 hours), plus the occurrence of postoperative low cardiac output (need for major inotropic support and/or use of intra-aortic balloon pump). Other outcome data included time on mechanical ventilation (hours), length of stay in the ICU (days), blood loss (milliliters in the first 12 postoperative hours), number of packed red blood cells transfused, peak postoperative serum creatinine value (milligrams per deciliter), postoperative creatinine clearance (milligrams per milliliter), acute renal failure (peak postoperative serum creatinine value 2 times the pre-

operative value and >2.0 mg/dl), low cardiac output (need for major inotropic support), intra-aortic balloon pump use, respiratory failure (prolonged mechanical ventilation due to poor gas exchange), ventricular arrhythmias, surgical re-exploration, sepsis, and mortality.

Details of the surgical technique have been previously reported.[4,5] Briefly, the procedure was conducted on an arrested heart with anterograde crystalloid or cold blood cardioplegia. Patients received crystalloid cardioplegia if the preoperative ejection fraction was >0.40 (n = 4, 13%). Therefore, the great majority of the patients received cold blood cardioplegia. Complete coronary revascularization was first performed, almost always with the left internal mammary artery on the left anterior descending coronary artery and sequential venous grafts on the right and circumflex coronary arteries, when needed. Since July 2001, we systematically introduced the use of a preshaped mannequin (TRISVR, Chase Medical, Richardson, Texas) filled at 50 to 60 ml/m^2 to optimize the size and shape of the new ventricle. The technique was a refinement of the Dor technique and allows for standardization of the procedure. Mitral valve repair, if needed, was performed using a previously described endoventricular technique.[6,7]

Data in tables and figures are presented as median and interquartile range or as number and percentage in the overall population and in patients with preoperative NT–pro-BNP ≤1,304 or >1,304 pg/ml, a cutoff based on the highest sensitivity and specificity determined as discussed below. Differences between the 2 groups were investigated using Student's *t* test for independent variables or Mann-Whitney test when appropriate, and a Pearson chi-square test. Logistic regression analysis and a receiver operating characteristics curve were used to evaluate factors significantly associated with a major morbidity. Accuracy of the model was tested by evaluating the area under the curve and calibration with a Hosmer-Lemeshow test. Adequate cut-off points were identified from the coordinates of the receiver operating characteristics curves; the cut-off values were settled at the point where the sum of sensitivity and specificity was the highest, according to the Youden index: (sensitivity + specificity) − 1. All analyses were performed using a computerized statistical package (SPSS 13.0, SPSS, Inc., Chicago, Illinois).

Results

NT–pro-BNP was higher than the normal upper limit (100 pg/ml) in 30 of the 31 patients with SVR at baseline. Particularly high values (>1,360 pg/ml) were observed in 42% of these patients (Table 1). The prevalence of many baseline patient characteristics that portend worse outcomes was greater in patients with higher NT–pro-BNP compared to those with lower values. Thus, these patients had higher EuroSCORE and lower ejection fraction.

Many in-hospital outcomes were significantly higher in patients with preoperative NT–pro-BNP >1,304 pg/ml compared to those with lower values (Table 2). Thus, these patients were more likely to manifest higher peak creatinine and lower creatinine clearance after surgery and had a longer length of mechanical ventilation and ICU stay. Low cardiac output state, renal failure, and need for intra-aortic balloon pump were threefold higher in this cohort. All patients but 2 with preoperative NT–pro-BNP >1,304 pg/ml had major morbidity in the postoperative period. The only death occurred in the group of patients with higher values. Length of stay in the ICU was on an average 3 days longer in these patients (7.2 ± 6.4 vs 4.1 ± 2.7).

Figure 1 shows the relation of preoperative NT–pro BNP levels to outcomes (logistic regression analysis) and suggests that increasing values were associated with greater morbidity in the early postoperative period. Figure 2 depicts the levels of NT–pro-BNP in patients with SVR with and

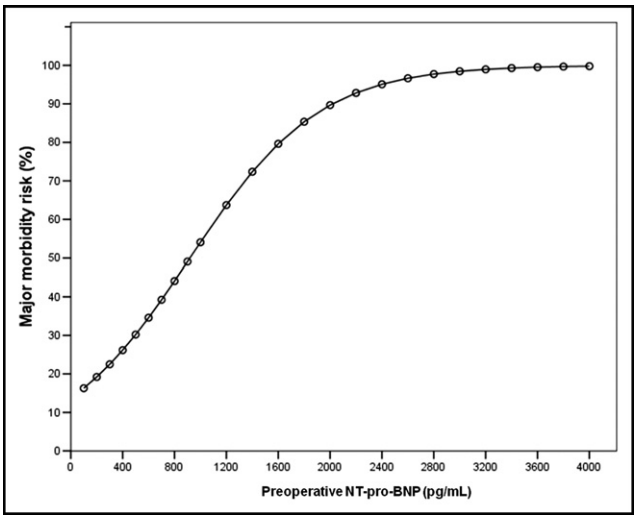

Figure 1. Relation between major morbidity risk and preoperative N-terminal pro–brain natriuretic peptide (logistic regression analysis).

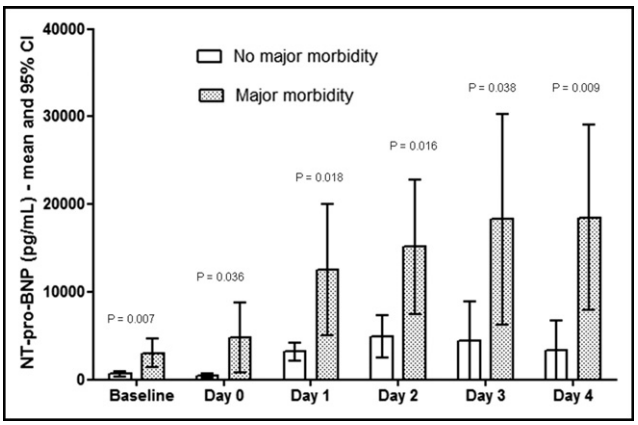

Figure 2. Time course of N-terminal pro–brain natriuretic peptide for the 2 groups. CI = confidence interval.

Table 3
Multivariable logistic regression analysis for major morbidity

Factor	B	SE	p Value	Odds Ratio	95% CI
Preoperative N-terminal pro–brain natriuretic peptide	0.002	0.001	0.032	1.002	1.001–1.003
Ejection fraction	−0.119	0.081	0.141	0.887	0.757–1.041
Constant	2.397				

B = regression coefficient; CI = confidence interval.

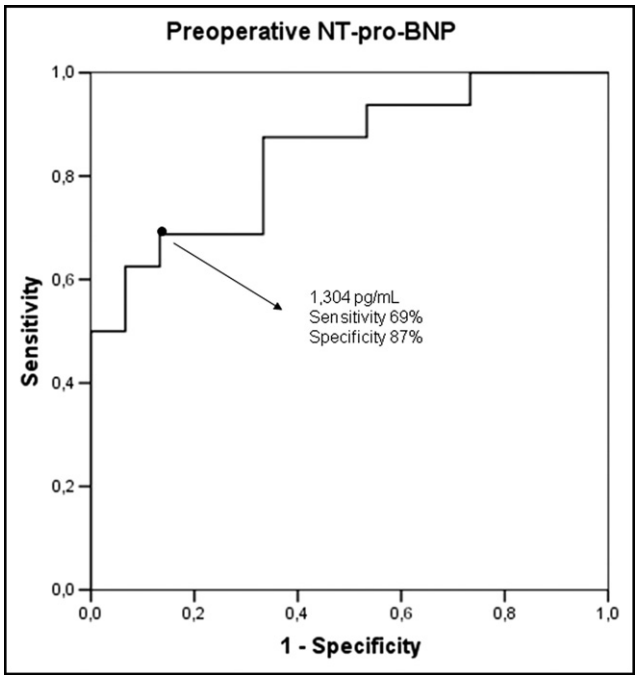

Figure 3. Receiver operating characteristics analysis applied to preoperative N-terminal pro–brain natriuretic peptide for exploring its accuracy in predicting major morbidity. The area under the curve for preoperative N-terminal pro–brain natriuretic peptide was 0.85 (95% confidence interval 0.67 to 1.04). A value of 1,304 pg/ml was associated with a sensitivity of 73% and specificity of 87% for major morbidity.

without major morbidity. As shown, at any given time point, values of NT–pro-BNP were three- to fivefold higher in patients with major morbidity compared to those without. Furthermore, although levels of NT–pro-BNP peaked on postoperative day 3 and then decreased in patients without major morbidity, these values continued to increase in those with major morbidity.

Results of logistic regression analyses are presented in Table 3. Preoperative NT–pro-BNP remained independently associated with major morbidity after accounting for major confounding, whereas lower left ventricular ejection fraction was marginally associated with this outcome. EuroSCORE was not significant in the multivariable analyses ($p = 0.535$). Hosmer-Lemeshow test confirmed a good calibration, with a chi-square value of 10.6 ($p = 0.223$). Thus, for each increase in preoperative NT–pro-BNP value by 1 pg/ml, the risk of major morbidity increased by 0.2%.

Results of receiver operating characteristics analysis applied to preoperative NT–pro-BNP for exploring its accuracy in predicting major morbidity are shown in Figure 3. The area under the curve for baseline NT–pro-BPN was 0.84 (95% confidence interval 0.70 to 0.98). A value of 1,304 pg/ml was associated with 68% sensitivity and 88% specificity for major morbidity (positive predictive value 85%, negative predictive value 72%).

Discussion

Our study evaluating the prognostic value of baseline NT–pro-BNP suggests that increased levels of this marker are common in patients undergoing SVR. Furthermore, levels >1,304 pg/ml were significantly associated with major morbidity. In fact, after accounting for major differences in baseline features (including left ventricular ejection fraction and EuroSCORE), NT–pro-BNP remained significantly and independently associated with major morbidity in patients undergoing SVR. Our data suggest that increasing or persistently high values of NT–pro-BNP are associated with poor short-term prognosis, whereas decreasing values perhaps may be a marker of satisfactory postoperative patient recovery. Thus, our study extends the prognostic value of NT–pro-BNP to patients undergoing SVR similar to that demonstrated in patients with congestive heart failure, acute coronary syndromes, and valvular heart disease.[8–13]

Few previous investigations have examined the role of NT–pro-BNP or BNP in patients with left ventricular systolic dysfunction undergoing CABG and/or SVR. Chello et al[14] evaluated 31 patients with left ventricular ejection fraction <35% undergoing CABG. They found that high baseline BNP levels decreased significantly at 10-month follow-up and correlated well with improvement in symptoms and left ventricular function. Schenk et al[1] studied 15 patients undergoing SVR, 5 of whom had BNP measured before and 3 months after surgery. They showed that BNP level decreased significantly after surgery and was associated with a trend for a decrease in left ventricular end-diastolic volume index. Suma et al[2] evaluated 36 patients with idiopathic dilated cardiomyopathy, with left ventricular end diastolic dimension >75 mm and akinetic septum, who underwent a septal anterior ventricular exclusion procedure. BNP decreased from 975 ± 866 to 404 ± 366 pg/ml at 1 month to 6 months. This decrease in BNP levels paralleled a decrease in left ventricular end-diastolic and end-systolic dimensions and end-diastolic pressure and an increase in left ventricular ejection fraction. Findings similar to these studies were demonstrated by Sartipy et al.[3] They evaluated 29 patients undergoing SVR at their institution and showed that there was a decrease in BNP and NT–pro-BNP that was associated with improvement in left ventricular ejection fraction and end-systolic and end-diastolic volumes. Taken together, data from these investigations suggest that there is consistent decrease in BNP and or NT–pro-BNP levels after SVR at intermediate-term follow-up that is associated with improved left ventricular remodeling, ejection fraction, and symptoms.

None of these studies measured these markers during the postoperative period of the index hospitalization and none evaluated the prognostic significance of baseline NT–pro-BNP.[1–3] Our data provide insight into these issues not addressed by these previous studies. Our findings support the short-term prognostic value of increased baseline NT–pro-BNP and help identify patients at increased risk of major morbidity in the postoperative period. Furthermore, these data indicate that following levels of NT–pro-BNP in the postoperative period may help distinguish between patients who are likely to recover from their operation soon and those who are not.

These data may have some clinical implications. In patients undergoing CABG, clinically overt heart failure before surgery has been shown to be associated with greater morbidity and mortality after surgery compared to patients without heart failure.[5] Clearly, preoperative NT–pro-BNP

provided important prognostic information even beyond that provided by left ventricular ejection fraction and/or clinical heart failure. This is not surprising given that NT–pro-BNP levels are increased in systolic and diastolic heart failure that is clinical detectable or overt.[8–10] Thus, NT–pro-BNP at baseline may be of potential value for risk assessment and for patient counseling of their perceived risk in those undergoing this procedure. Furthermore, the serial measurements of this marker to guide therapy in patients with congestive heart failure have been shown to improve outcomes.[15] Whether a similar decrease in pre- and postoperative volume overload with appropriate therapy guided by and/or targeted to decrease NT–pro-BNP will improve outcomes of patients undergoing SVR remains to be proved in the future.

Our study findings should be interpreted in light of its limitations. This was a retrospective study involving a small number of patients. Thus, our data should be regarded as hypothesis generating and inferences regarding "cause and effect relation" or any therapeutic implications should be made with caution. Clearly, these findings need confirmation in future studies in a larger number of patients. We are unable to provide insight into the association of SVR with longer-term changes in NT–pro-BNP or outcomes.

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