N-Terminal pro-Brain Natriuretic Peptide as a Useful Biomarker for Monitoring Prognosis in Patients With Cardiac Valve Replacement

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Background: N-terminal pro-Brain natriuretic peptide (NT-proBNP) is an important biomarker to indicate cardiac function, but its significance in cardiac surgery is still unclear. **Objective:** To explore clinical significance of serum NT-proBNP and their dynamic characteristics in patients with cardiac valve replacement (CVR). **Methods:** Dynamically detecting pre-operative and postoperative serum NT-proBNP on Elecsys 2010 in 60 CVR patients. **Results:** (1) There was a good relationship between pre-operative NT-proBNP and pre-operative NYHA classification, ejection fraction, fractional shortening, or between postoperative 1 day log [NT-proBNP] and postoperative ICU time, correlation coefficients were respectively 0.426 ($P = 0.001$), -0.465 ($P = 0.001$), -0.463 ($P = 0.002$), and 0.453 ($P = 0.006$). (2) Pre-operative NT-proBNP would be higher in multivalves damage or mitral lesions patients than that in single valve damage or aortic lesions. It indicated NT-proBNP $> 1,352$ pg/ml could discriminate multivalves damage in

Rheumatic Heart Diseases (RHD) patients (sensitivity: 0.742; specificity: 0.64); and NT-proBNP > 549.12 pg/ml could differentiate mitral lesions and aortic lesions (sensitivity: 0.92; specificity: 0.75). However, pre-operative serum NT-proBNP for differentiating atrial fibrillation and sinus arrhythmia was not most efficient (AUC = 0.655; $P = 0.044$). (3) Perioperative NT-proBNP in CVR patients was characterized by early postoperative NT-proBNP increasing and late postoperative NT-proBNP decreasing. The peak of postoperation NT-proBNP was at postoperative 7 days. **Conclusions:** Serum NT-proBNP was not only a good biomarker to effectively evaluate heart function but also to evaluate the cardiac valve damage in RHD patients, and post-operative NT-proBNP dynamic determination, especially detecting postoperative 1 day, 7 days and 14 days NT-proBNP would be more useful to evaluate prognosis of CVR patients. *J. Clin. Lab. Anal.* 25:149–155, 2011. © 2011 Wiley-Liss, Inc.

Key words: cardiac valve replacement; N-terminal pro-brain natriuretic peptide; NT-proBNP; rheumatic heart diseases

INTRODUCTION

N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) is a new and important biomarker. Clinical application of NT-proBNP in diagnosing heart failure and differentially diagnosing cardiac or noncardiac acute dyspnea has been clearly demonstrated and widely used (1–4). The significance of NT-proBNP in cardiac surgery is becoming more attractive now, but there are limited data regarding the utility of NT-proBNP in patients undergoing cardiac surgery.

NT-proBNP has longer half-time than Brain Natriuretic Peptide (BNP), and both of them could be influenced by ventricular volume expansion and ventricular pressure overload (5–7). In patients with cardiac valve lesions, the

abnormal ventricular volume or overload pressures could cause the abnormal NT-proBNP and BNP expression. Because NT-proBNP was more stable and more sensitive in blood samples than BNP, here we paid more attention to serum NT-proBNP expression in patients with cardiac valve replacement (CVR) and illustrated the dynamic

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characteristics of perioperative serum NT-proBNP in CVR in order to explore the following questions:

1. Could perioperative serum NT-proBNP predict the prognosis of CVR patients?
2. Could pre-operative serum NT-proBNP indicate heart function and cardiac valve damage in rheumatic heart diseases (RHD)?

SUBJECTS AND METHODS

Subjects

We retrospectively studied 60 patients (56 with RHDs (93%), 4 with congenital heart diseases (7%)) who were treated by CVR in our hospital from January 2007 to February 2008 (23 males (38%) and 37 females (62%), age from 16 to 66 years, mean age 45.20 years). Among these patients there were 25 patients (41%) with single valve damage (including 12 patients with mitral lesions, 12 with aortic lesions, 1 with atrial or ventricular septal defect), 31 patients (52%) with multivalves damage (including double or triple valves damage) and 4 patients (7%) with valve damage combined thrombus. According to heart rhythm classification, there were 27 patients (45%) with sinus arrhythmia (SA), 31 patients (52%) with atrial fibrillation (AF), 2 patients (3%), respectively, with atrialflutter and junctional rhythms. Clinical characteristics of CVR patients were shown in Table 1. During operation aortic cross-clamping was made and the aortic cross-clamping time ranged from 13 to 113 min, mean time 60 min. All patients were cured or better after CVR. Pre-operative and postoperative time

points in detecting serum NT-proBNP were, respectively, 3 days before CVR, postoperation 1, 2, 3, 4, 5, 6, 7, 14, 21, 30 days, and more than 90 days. Before operation all patients were made heart function categories by New York Heart Association (NYHA) criteria (3 patients (5%) with NYHA I, 13 patients (22%) with NYHA II, 41 patients (68%) with NYHA III, 3 patients (5%) with NYHA IV), and their clinical relative determinations were made by Doppler echocardiography, including ejection fraction (EF) (ranged from 29 to 83%, mean 58.57%), fractional shortening (FS) (ranged from 14 to 52%, mean 33%), left ventricular end systolic pressure (LVESP) (ranged from 12 to 24 mmHg, mean 16 mmHg), left ventricular end diastolic pressure (LVEDP) (ranged from 6 to 14 mmHg, mean 10 mmHg), and left ventricular end diastolic diameter (LVEDD) (ranged from 26 to 83 mm, mean 51 mm).

Excluding criteria: patients with renal dysfunction.

Serum NT-proBNP Detection

All samples were prepared and detected according to clinical operation standards. Sera were isolated from 5 ml nonanticoagulation blood samples in 2 hr. Apply electrochemiluminescence immunoassay apparatus Elecsys 2010 (Roche Diagnostics, Mannheim, Germany) to detect serum NT-proBNP as clinical routine samples. The unit of NT-proBNP is pg/ml.

Statistics

All data were analyzed by SPSS 11.0 statistic software and were plotting with GraphPad Prism software. Data

TABLE 1. Clinical Characteristics of Cardiac Valve Replacement Patients

	<i>n</i>	Age (mean ± SD)	Sex (male:female)	EF(%) (mean ± SD)	Patients with cardiac valve replacement			
					NYHA classification			
					I	II	III	IV
All patients	60	45.20 ± 11.77	23:37	58.57 ± 13.25	3	13	41	3
<i>Classification by underlined diseases</i>								
Rheumatic heart diseases	56	45.68 ± 10.67	21:35	58.67 ± 13.39	1	13	40	2
Congenital heart diseases	4	38.50 ± 23.92	2:2	55.25 ± 5.38	2	0	1	1
<i>Classification by valve damages</i>								
Single valve damage	25	45.16 ± 15.23	12:13	60.92 ± 9.36	1	7	14	0
Mitral lesions	12	50.08 ± 8.85	5:7	57.99 ± 9.93	0	0	12	0
Aortic lesions	12	42.58 ± 17.95	7:5	62.52 ± 8.61	1	6	2	0
Atrial or ventricular septal defect	1	17.00	0:1	71.20	0	1	0	0
Multivalves damage	31	45.39 ± 9.05	11:20	56.85 ± 14.07	0	5	23	2
Valve damage combined thrombus	4	44.00 ± 6.68	0:4	54.33 ± 24.38	0	1	3	0
<i>Classification by heart rhythm</i>								
Sinus arrhythmia	27	43.96 ± 14.66	11:16	62.73 ± 13.45	3	11	11	2
Atrial fibrillation	31	45.81 ± 8.91	11:20	54.60 ± 12.50	0	2	28	1
Other heart rhythms	2	52.50 ± 6.36	1:1	62.55 ± 10.68	0	0	2	0

EF = ejection fraction; NYHA = New York Heart Association.

were described by median, interquartile range for original NT-proBNP results and mean $\pm$ standard deviation (SD) for logarithmic transformed data. Logarithmic transformed NT-proBNP data were in normal distribution, which showed greater statistic power and was more suitable for parameter tests. One-way ANOVA test or *t*-test was done for group comparison, and Dunnett T3 test or LSD test was done for comparison with each other; Spearman correlation and Receiver Operating Characteristic (ROC) analysis was made. $P < 0.05$ was considered significant.

RESULTS

Relationship Between Perioperative Serum NT-proBNP and Clinical Cardiac Function Determinations

There was a good relationship between pre-operative serum NT-proBNP and pre-operative NYHA classification, EF, FS, and spearman correlation coefficients (r_s) were 0.426 ($P = 0.001$), -0.465 ($P = 0.001$) and -0.463 ($P = 0.002$), respectively. Besides, there was no relationship between pre-operative NT-proBNP and LVEDD, LVESP or LVEDP, r_s were 0.151 ($P = 0.25$), -0.173 ($P = 0.187$), and -0.105 ($P = 0.423$), respectively.

A good correlation between postoperative 1 day log [NT-proBNP] and postoperative intensive-care unit (ICU) time ($r = 0.453$, $P = 0.006$) was shown, in scatter graph the coefficient of determination (R^2) between them was 0.205 ($P = 0.006$) (Fig. 1A). But there was no correlation between NT-proBNP and postoperation hospitalizing time or aortic cross-clamping time

($r_s = -0.093$ [$P = 0.595$]; 0.071 [$P = 0.708$], respectively). In ICU time > 60 hr group postoperative serum NT-proBNP significantly was higher than other groups (Fig. 1B). But there was no correlation between pre-operative NT-proBNP level and postoperative ICU time.

Serum NT-proBNP Detection in Patients With Different Cardiac Valve Lesions

Pre-operative serum NT-proBNP in patients with double valves or triple valves damage was significantly higher than that in single valve damage (P value was, respectively, 0.021 or 0.002), and there was no difference between double valves damage group and triple valves damage group ($P = 0.415$). In different types of single valve damage serum NT-proBNP level was different, NT-proBNP in patients with mitral lesions was higher than that in aortic lesions whatever in pre-operation or in postoperation ($P = 0.008$ or $P = 0.020$, respectively) (Table 2). ROC analysis showed that the cutoff of pre-operation serum NT-proBNP to differentiate single valve or multivalve damage was 1,352 pg/ml (sensitivity: 0.742; specificity: 0.64); and the cutoff to differentiate mitral lesions and aortic lesions was 549.12 pg/ml (sensitivity: 0.92; specificity: 0.75) (Fig. 2).

Serum NT-proBNP in Patients With AF or SA

Pre-operative serum NT-proBNP was significantly higher in patients with AF than that in SA patients ($P = 0.008$); however, there was no significant difference in postoperation NT-proBNP between them

Fig. 1. Association between postoperative Serum NT-proBNP and ICU time. (A) The scatter graph showed the correlation between postoperative 1 day serum NT-proBNP and ICU time. Line regression analysis showed that R^2 was 0.205 ($P = 0.006$). (B) With the ICU time increasing, postoperative 1 day serum NT-proBNP gradually increased. When ICU staying time was more than 60 hr, serum NT-proBNP would sharply increase.

TABLE 2. Serum NT-proBNP in CVR Patients With Single Valve or Multivalves Damage

Group	N	Pre-operative NT-proBNP		Postoperative 1 week NT-proBNP	
		(pg/ml) Median (interquartile range)	Logarithmically transformed value (mean $\pm$ SD)	(pg/ml) Median (interquartile range)	Logarithmically transformed value (mean $\pm$ SD)
Single valve damage	25	716.70 (142.80–2,346.50)	2.79 $\pm$ 0.70	2,021.00 (1,000.00–4,549.00)	3.31 $\pm$ 0.48
Mitral lesions	12	1,526.00 (804.03–3,538.00) [†]	3.20 $\pm$ 0.42 [†]	3,129.50 (1,460.00–6,656.50) [†]	3.56 $\pm$ 0.42 [†]
Aortic lesions	12	189.55 (111.45–1,391.73)	2.51 $\pm$ 0.68	1,240.00 (620.93–3,256.00)	3.13 $\pm$ 0.41
Double valves damage	24	2,260.50 (826.48–3,782.50)*	3.26 $\pm$ 0.41*	3,358.00 (1,702.75–7,393.75)	3.52 $\pm$ 0.36
Triple valves damage	7	3,000.00 (2,402.00–3,301.00)*	3.44 $\pm$ 0.23*	4,007.00 (2,672.00–4,752.00)	3.60 $\pm$ 0.14

Note: Statistical significance marker based on the parameter tests results.

* $P < 0.05$, compared with single valve damage group.

[†] $P < 0.05$, compared with aortic lesions group.

CVR = cardiac valve replacement.

Fig. 2. ROC analysis of pre-operative NT-proBNP for differentiating valve damages in CVR patients. (A) ROC for differentiating multivalve or single valve damage (AUC = 0.728, $P = 0.004$). (B) ROC for differentiating mitral or aortic lesions (AUC = 0.799, $P = 0.013$). (C) ROC for differentiating AF or SA (AUC = 0.655, $P = 0.044$).

TABLE 3. Serum NT-proBNP Analysis in CVR Patients With Atrial Fibrillation or Sinus Arrhythmia

Group	N	Pre-operative NT-proBNP		Postoperative 1 week NT-proBNP	
		(pg/ml) Median (interquartile range)	Logarithmically transformed value (mean $\pm$ SD)	(pg/ml) Median (interquartile range)	Logarithmically transformed value (mean $\pm$ SD)
Atrial fibrillation	31	2,328.00 (993.00–3,048.00)*	3.29 $\pm$ 0.34*	2,672.00 (1,847.00–6,847.00)	3.54 $\pm$ 0.35
Sinus arrhythmia	27	616.90 (159.90–3,301.00)	2.85 $\pm$ 0.74	2,819.00 (1,104.00–5,103.00)	3.34 $\pm$ 0.44

Note: Statistical significance marker based on the parameter tests results.

* $P < 0.05$, compared with sinus arrhythmia group.

CVR = cardiac valve replacement.

($P = 0.068$) (Table 3). The underlined diseases of patients with AF included mitral lesions (29%) and multivalve damage (71%); and the major underlined diseases of patients with SA included aortic lesions (44.44%) and other valve damage. ROC of pre-operative serum NT-proBNP for differentiating AF and SA showed area under curve (AUC) was 0.655 ($P = 0.044$) (Fig. 2).

Perioperative Dynamic Characteristics of Serum NT-proBNP in CVR Patients

Postoperative 1 day serum NT-proBNP was significantly higher than pre-operative one ($P = 0.002$). Postoperative serum NT-proBNP increased and at postoperative 1 week to the peak, then decreased with time going, until postoperative more than 3 months

TABLE 4. Serum NT-proBNP Dynamic Analysis in Patients With CVR

Group	N	Serum NT-proBNP	
		(pg/ml) Median (interquartile range)	Logarithmically transformed value (mean $\pm$ SD)
Pre-operation	60	1,708.50 (591.93–3,144.00)*	3.09 $\pm$ 0.59*
Postoperative 1 week	60	2,643.50 (1,320.50–5,553.75)†	3.44 $\pm$ 0.40†
Postoperative 2 weeks	33	2,495.00 (1,266.00–3,369.50)†	3.34 $\pm$ 0.40†
Postoperative 3 weeks	25	1,970.00 (930.75–2,778.50)	3.21 $\pm$ 0.38
Postoperative 4 weeks	25	1,431.00 (675.30–2,574.50)	3.16 $\pm$ 0.41
Postoperative more than 3 months	10	412.05 (229.53–1,179.00)	2.66 $\pm$ 0.49

Note: Statistical significance marker based on the parameter tests results.

* $P < 0.05$, compared with postoperative 1 week.

† $P < 0.05$, compared with postoperative more than 3 months.

CVR = cardiac valve replacement.

serum NT-proBNP was significantly lower than that at postoperative 1 week ($P = 0.008$). The whole procedure of postoperative NT-proBNP decreasing could be divided into two parts. In the first part (from postoperative 1 week to postoperative 4 weeks) the decreasing of NT-proBNP was a gentle slope, and in the second part (from postoperative 4 weeks to postoperative more than 3 months) the decrease was a steep slope (Table 4 and Fig. 3A).

Further analysis of the ratio of postoperative NT-proBNP/pre-operative NT-proBNP in CVR patients showed there was a similar trend with perioperative serum NT-proBNP levels during postoperative more than 1 month (long-term dynamic analysis) (Fig. 3C). However, there was difference in postoperative 1 week (short-term) dynamic analysis between the ratio of postoperative NT-proBNP/pre-operative NT-proBNP and postoperative serum NT-proBNP (Fig. 3B and D). It was shown that serum NT-proBNP level in postoperative 3 and 4 days decreased strikingly, and ratio value reached to the peak in postoperative 4 days, which indicated that in short-term dynamic analysis there was some fluctuation and the ratio of postoperative NT-proBNP/pre-operative NT-proBNP could be better to demonstrate the dynamic characteristics in CVR with balancing pre-operative NT-proBNP level, without indicating serum NT-proBNP values. There was no significant difference in serum NT-proBNP level or ratio value among the seven groups ($P = 0.320$ and $P = 0.463$, respectively).

DISCUSSION

Serum NT-proBNP or BNP was considered as a useful clinical biomarker in heart failure, and their clinical application in surgery was rare. Some researches indicated that BNP was useful in patients with cardiac surgery (8,9), and others thought that BNP level after cardiac surgery was nonspecifically influenced by many

perioperative variables, and would increase in any corrective surgeries (10,11). In this study we chose more stable serum NT-proBNP to detect and explore clinical significance of serum NT-proBNP in cardiac surgery to conquer the shortcomings of BNP. In order to exclude the influence of renal dysfunction on serum NT-proBNP, we just included CVR patients with normal renal function in our research, because NT-proBNP was mainly cleared through the kidney (12).

In this study, it first showed that serum NT-proBNP was a good biomarker to effectively evaluate heart function in CVR patients as its application in heart failure. In CVR patients pre-operative NT-proBNP was correlated with pre-operative EF, FS or NYHA classification. The worse heart function, the higher serum NT-proBNP would be. However, we didn't find the correlation between pre-operative or postoperative serum NT-proBNP and LVESP, LVEDP, or LVEDD, which was similar to the results of Saribulbul in cardiac surgery (9). But Pudil et al. and Tretjak et al. showed that there was significant correlation between NT-proBNP and LVEDD in patients with heart failure (13,14). We speculated that in patients with cardiac surgeries heart function was influenced by more factors and could become left or right or whole ventricular dysfunction, so LVEDD would not the main factor to influence serum NT-proBNP, and there was no correlation between them any more; however, in heart failure (ventricular dysfunction) LVEDD could reflect heart function and be a main factor to influence serum NT-proBNP.

Here we found that there was no correlation between pre-operative or post-operative NT-proBNP and aortic cross-clamping time in CVR, which was similar to other results (15–18), but it was different from the results of Berendes et al. or Rafal et al. (8,19). Their studies showed that BNP correlated with aortic cross-clamping time. We thought the different results may be derived from the difference of determinations, cardiac surgery techniques and cardiac surgery types.

Fig. 3. Perioperative serum NT-proBNP dynamic characteristics in CVR patients. (A) Serum NT-proBNP level changing from pre-operation to postoperative more than 3 months. (B) Serum NT-proBNP level changing in postoperative 1 week. In both of them X-axis showed time points, and Y-axis showed mean logarithmical value of NT-proBNP concentration. (C) The ratio of postoperative NT-proBNP/pre-operative NT-proBNP changing from pre-operation to postoperative more than 3 months. (D) The ratio of postoperative NT-proBNP/pre-operative NT-proBNP changing in postoperative 1 week. In both of them X-axis showed time points, and Y-axis showed ratio value.

Second, we found that serum NT-proBNP could effectively evaluate the cardiac valve damage in RHD patients. It was observed that there was higher pre-operative serum NT-proBNP in patients with mitral damage or AF. The similar phenomena have also been observed in other researches—high serum NT-proBNP existed in pulmonary hypertension which was closely related to the mitral lesions (20–22) and higher NT-proBNP could be observed in AF than that in sinus rhythm (23). ROC analysis indicated that NT-proBNP could be a useful biomarker to evaluate heart function and valve damage in RHD patients. When pre-operative serum NT-proBNP was more than 1,350 pg/ml in patients with RHD, it could indicate that they suffered from cardiac multivalve damage; in patients with single

valve damage, when serum NT-proBNP was more than 550 pg/ml, it could indicate that the patients suffered from mitral lesions. But pre-operative serum NT-proBNP could not effectively indicate AF in RHD patients.

Finally, our study indicated that postoperative NT-proBNP level dynamic determination would be useful to evaluate prognosis of CVR patients, and in dynamic analysis ratio of postoperative NT-proBNP/pre-operative NT-proBNP would be better to demonstrate the change of perioperative serum NT-proBNP, but ignoring their concentration changes. Here we showed that in early stage after CVR NT-proBNP would increase due to the surgery damage, and with time going NT-proBNP decreased. In this study, all the patients were better or cured after operation; it was

believed that dynamic decreasing of postoperative serum NT-proBNP could predict the good prognosis of CVR patients, especially serum NT-proBNP determination in postoperative 1 day, 7 days and 14 days was useful and economic. However, here we just analyzed serum NT-proBNP after postoperative 1 day; the clinical significance of serum NT-proBNP during postoperative 24 hr still needed to be further verified.

CONCLUSIONS

In CVR patients, serum NT-proBNP was not only a good biomarker to effectively evaluate heart function but also to evaluate the cardiac valve damage in RHD patients, and postoperative NT-proBNP dynamic determinations would be more useful to evaluate prognosis of CVR patients.

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