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The Role of Serial NT-ProBNP Level in Prognosis and Follow-Up Treatment of Acute Heart Failure after Coronary Artery Bypass Graft Surgery

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Abstract

BACKGROUND: After coronary artery bypass graft (CABG) surgery, heart failure is still major problem. The valuable marker for it is needed.

AIM: Evaluating the role of serial NT-proBNP level in prognosis and follow-up treatment of acute heart failure after CABG surgery.

METHODS: The prospective, analytic study evaluated 107 patients undergoing CABG surgery at Ho Chi Minh Heart Institute from October 2012 to June 2014. Collecting data was done at pre- and post-operative days with measuring NT-proBNP levels on the day before operation, 2 hours after surgery, every next 24 h until the 5th day, and in case of acute heart failure occurred after surgery.

RESULTS: On the first postoperative day (POD1), the NT-proBNP level demonstrated significant value for AHF with the cut-off point = 817.8 pg/mL and AUC = 0.806. On the second and third postoperative day, the AUC value of NT- was 0.753 and 0.751. It was statistically significant in acute heart failure group almost at POD 1 and POD 2 when analyzed by the doses of dobutamine, noradrenaline, and adrenaline (both low doses and normal doses).

CONCLUSION: Serial measurement of NT-proBNP level provides useful prognostic and follow-up treatment information in acute heart failure after CABG surgery.

Introduction

Acute heart failure emerged as the primary cause of mortality after heart surgery in general and CABG surgery in particular [1]. It needs to early recognize before operation that helps clinicians consider patients who had heart failure into subgroups and allocate resources to maximize benefit from treatment and minimize risks such as adverse events. To predict early outcomes from cardiac surgery, both clinical tools (scoring systems) and biochemical tests were used. The two most common scoring systems were the EuroSCORE [2] and the Parsonnet score [3]. Although frequently used, it also had some limitations [4], [5]. To resolve, some biochemical tests were considered. Among that, NT-proBNP was emerged as one of the promise markers in heart disease, especially in heart failure [6]. It was used to predict postoperative outcomes in heart surgery in both early [7] and long-term effects [8]. The Canadian guideline recommended using it in persons with HF as a prognostic factor [9].

The guideline of ESC also remarked NT-proBNP as one of prognostic factors [10]. Moreover, in CABG surgery, it independently predicted postoperative outcome [11]. In combination with existing clinical tools such as EuroSCORE II, it showed more accuracy than using it alone [12].

Besides predictive ability before cardiac surgery [13], NT-proBNP levels contribute a valuable role in heart failure management [14] evenly in acute or unstable state [15]. Elevating NT-proBNP levels in these situations was associated with poor clinical outcomes [16], [17]. To optimize medical therapy, serial NT-proBNP measurement was used in stable CHF patients [18]. But in acute heart failure after CABG surgery, data of this biochemical marker were too limited.

Therefore, this study aimed to evaluate the serial NT-proBNP level that could provide prognostic and follow-up treatment information of acute heart failure after CABG surgery.

Materials and Methods

We conducted this prospective study on 107 patients who underwent CABG surgery at Ho Chi Minh Heart Institute from October 2012 to June 2014. Inclusion criteria included patients with established diagnoses of coronary artery stenosis based on angiography; aged 18 and older; consultation of internal medicine and surgery, and indication for CABG according to the recommendation American Internal Medicine Association (ACC/AHA/ACP /ASIM).

The exclusion criteria were: aged <18; damage of 1 or 2 branches of coronary artery; overall 50 - 60% of coronary artery stenosis with excepting main body; < 50% diameter of coronary artery stenosis; concomitant cardiac surgery such as valve surgery and septal surgery ; renal function insufficiency (eGFR <30 ml/min/1.73m^2).

Monitoring

Chronic heart failure (CHF) before surgery was diagnosed according to the Framingham criteria, while postoperative diagnosis of acute heart failure (AHF) was followed the guidelines of Viet Nam Heart Association 2015 with staging A, B, C and D according to ACC/AHA and grading according to NYHA. Indexes in heart failure were recorded in echocardiography. The main prognosis factor of heart failure after surgery were EuroSCORE and the level of serial NT-proBNP. NT-proBNP level was quantified at the Department of Biochemistry at Ho Chi Minh Heart Institute, using the electrochemiluminescence immunoassay (ECLIA). The optimal cutting points of NT-proBNP to determine acute heart failure for ages younger than 50, from 50 to 75 and older than 75 years are 450, 900 and 1800 pg/ml, respectively. The NT-proBNP-independent age cut point less than 300 pg/ml had a negative diagnostic value to rule out acute heart failure at 98%.Collecting time was noted as following: B0: the day before surgery; B1: 2 hours after surgery; B2, B3, B4, B5 were collected at 8 a.m on days 2, 3, 4, 5 after surgery; Bx: at the time of expression of cardiac dysfunction (continuous monitoring of cardiac index on the Flo-Trac system) or when the patient presents with acute heart failure.

We also recorded data about dosage and using time of dobutamine, noradrenaline, and adrenaline in collecting time after surgery to follow-up treatment. Collecting time was noted as following: N0: the day before surgery; N1: 2 hours after surgery; N2, N3, N4, N5 were collected at 8 a.m on days 2, 3, 4, 5 after surgery. In addition, follow-up at times when patients showed cardiac impairment or when acute heart failure occurred.

Statistical analysis

Statistical analysis was performed by Epidata 6 and STATA version 14.0 software.

Descriptive analysis presented as mean ± standard deviation (95% confidence interval). Testing t-Student/Mann-Withney U test/Wilcoxon/ANOVA and Chi-square/ Fisher's exact test, Kolmogorov test, Person correlation, single and multivariate linear regression methods used in the study. p-value < 0.05 was known as statistically significant.

Results

Out of 107 patients, 67.3% was male. Medical history was chest pain (98.1%), hypertension (77.6%), myocardial ischemia (77.6%), heart failure (28.0%), diabetes (24.3%), myocardial infarction (9.4%), dyslipidemia (7.5%), arrhythmias (4.7%), COPD (3.7%), and renal failure (1.9%). Demographics of CHF before surgery and AHF after surgery showed in Table 1.

Table 1: Demographics of chronic heart failure before surgery and acute heart failure after surgery

Pre-operative condition	Post-operative condition			
	Without AHF	AHF	Total	p-value
Without CHF	64 (78.1 %)	7 (28.0 %)	71 (66.4 %)	< 0.0001
CHF	18 (21.9 %)	18 (72.0 %)	36 (33.6 %)	< 0.0001
Total	82 (76.6 %)	25 (23.4 %)	107 (100%)	< 0.0001

Note: CHF: Chronic heart failure; AHF: Acute heart failure.

On the first postoperative day (POD1), the NT-proBNP level demonstrated significant value for AHF in patients undergoing CABG surgery with the cut-off point = 817.8 pg/mL and AUC = 0.806 (95% CI = 0.71 to 0.90; p<0.0001; sensitivity = 70%; and specificity = 80.5%). The values of NTproBNP for AHF on the second and third postoperative days (POD 2 and POD3) showed detail in Table 2.

Table 2: Cut-off values of NT-proBNP according to Euro-score

Post-operative day (POD)	Cut-off value	Sensitivity	Specificity	AUC (95% CI)	Youden – Index
POD 1	817.8	70.0 %	80.5 %	0.806 (0.71 – 0.90)	0.505
POD 2	2,516	66.7 %	77.9 %	0.753 (0.64 – 0.87)	0.446
POD 3	3,556	60.0 %	81.6 %	0.751 (0.64 – 0.86)	0.416

Note: AUC: Area under the curve; CI: Confidence Interval.

Table 3 performed detail analysis of NT-proBNP cut-off value according to EuroSCORE.

Table 3: Detail analysis of cut-off value of NT-proBNP according to EuroSCORE

		EuroSCORE						Cut-off NT-proBNP					
		L and I risk	High risk	Indexes				≤ Cut-off	> Cut-off	Indexes			
				Sen	Spe	Acc	P-value			Sen	Spe	Acc	P-value
Pre-operative	Without CHF (71)	58 (81.7)	13(18.3)	47.2	81.7	70.1	0.002	56 (78.9)	15 (21.1)	80.6	78.9	79.44	0.000
Cut-off (508.8 pg/ml)	CHF (36)	19 (52.8)	17 (47.2)					7 (19.4)	29 (80.6)				
POD 1 Cut-off	No AHF (94)	73 (77.7)	21 (22.3)	77.7	69.2	76.64	0.002	70 (74.5)	24 (25.5)	74.5	92.3	76.64	0.000
(871.8 pg/ml)	AHF (13)	4 (30.8)	9 (69.2)					1 (7.7)	12 (92.3)				
POD 2 Cut-off	No AHF (98)	74 (75.5)	24(24.5)	75.5	66.7	74.8	0.014	68(69.4)	30(30.6)	69.4	77.8	70.1	0.008
(2516 pg/ml)	AHF (9)	3 (33.3)	6 (66.7)					2(22.2)	7 (77.8)				
POD 3 Cut-off	Without AHF(104)	76(73.1)	28(26.9)	66.7	73.1	72.9	0.189	74(71.8)	29(28.2)	100	71.8	72.6	0.026
(3556 pg/ml)	AHF (3)	1 (33.3)	2 (66.7)					0 (0)	3 (100)				

Note: Sensitivity = Sen; Specificity = Spe ;Accurac = ACC , POD: Postoperative day; CHF: Chronic heart failure; AHF: Acute heart failure; Low and Intermediate risk = L and I risk.

To follow-up treatment, the general dosage and using time of inotrope was shown in Table 4.

Table 4: Dosage and using time of inotrope (µg/kg/min)

Factors		Post-operative condition		p-values
		Without AHF (n=82)	AHF (n=25)	
Noradrenalin	Dosage	0.85 ± 1.59	0.14 ± 0.12	0.75^{f}
	Using time	43.1 ± 28.9	112.9 ± 37.5	0.000^{c}
Dobutamine	Dosage	3.32 ± 1.82	6.25 ± 2.47	0.000^{f}
	Using time	29.1 ± 28.2	101.1 ± 47.3	0.000^{f}
Adrenalin	Dosage	0.026 ± 0.048	0.15 ± 0.15	0.000^{f}
	Using time	16.6 ± 30.7	82.9 ± 55.6	0.000^{f}

Note: AHF: Acute heart failure.

More detail showed in Table 5 (dobutamine), table 6 (noradrenaline), and table 7 (adrenaline). The level of NT-proBNP level in AHF group was statistically significant compared to the without AHF group at POD 1 and POD 2 when analyzed by the normal doses of dobutamine. In low doses, it just showed statistically significant at POD 2 (Table 5). In AHF group it was statistically significant compared to the without AHF group at POD 1 and POD 2 when analyzed by the low doses of noradrenaline. In low doses, it did not show statistically significant at POD all three days after surgery (Table 6).

Table 5: Level of serum NT-proBNP and dobutamine doses

Time	Dobutamin doses	Post-operative condition		p-values
		Without AHF	AHF	
POD 1	Low doses (< 5 µg)	496.1 ± 609.9	2885	0.1^{f}
	Normal doses (5-15 µg)	1.077.5 ± 2.154.5	2.499.8 ± 1.646.7	0.000^{f}
	p-values	0.041^{f}	0.59^{f}	
POD 2	Low doses (< 5 µg)	1.956.8 ± 1.728.9	6.088 ± 4.774.8	0.023^{f}
	Normal doses (5-15 µg)	3.465.2 ± 3.224.7	9.387.5 ± 8.623.8	0.036^{f}
	p-values	0.049^{f}	0.796^{f}	
POD 3	Low doses (< 5 µg)	3.653.3 ± 4.984.2		
	Normal doses (5-15 µg)	5.797.8 ± 3.937	8.123.7 ± 4.636.0	0.393^{f}
	p-values	0.001^{f}		

Note: POD: Post-operative day; AHF: Acute heart failure.; f. Mann-Withney U test.

When analyzed by the normal doses of adrenaline, in AHF group it was statistically significant compared to the without AHF group at POD 1 and POD 2.

Table 6: Level of serum NT-proBNP and noradrenalin doses

Time	Noradrenalin dosage	Post-operative condition		p-values
		Without AHF	AHF	
POD 1	Low dosage (<0.01 µg)	862.7 ± 1.855.5	2.447.2 ± 628.5	0.0001^{f}
	Normal dosage (≥0.01 µg)	749.8 ± 871.9	2.578.7 ± 2.172.9	0.062^{f}
	p-values	0.7^{f}	0.81^{f}	
POD 2	Low dosage (<0.01 µg)	2.335.5 ± 2.436.2	9.252.8 ± 9.681.3	0.014^{f}
	Normal dosage (≥0.01 µg)	3.509 ± 2751.1	7.081.3 ± 4.235.8	0.073^{f}
	p-values	0.03^{f}	0.807^{f}	
POD 3	Low dosage (<0.01 µg)	3.952.7 ± 5.067.4	13.415	0.13^{f}
	Normal dosage (≥0.01 µg)	5.804.9 ± 3.476.9	5.478 ± 994.2	0.89^{f}
	p-values	0.003^{f}	0.221^{f}	

Note: POD: Post-operative day; AHF: Acute heart failure.; f. Mann-Withney U test.

It is statistically significant in POD 2 and POD 3 when analyzed by the low doses of adrenaline (Table 7).

Table 7: Level of serum NT-proBNP and adrenalin doses

Time	Adrenalin	Post-operative condition		p-values
		Without AHF	AHF	
POD 1	Low dosage (<0.05 µg)	585.3 ± 726.6	2.595	0.12^{f}
	Normal doage (≥0.05)	1.444.4 ± 2.911	2.523.9 ± 1.650.3	0.004^{f}
	p-values	0.051^{f}	1^{f}	
POD 2	Low dosage (<0.05 µg)	1.855.6 ± 1.725.2	2.733.8 ± 8.32.3	0.07^{f}
	Normal doage (≥0.05)	4.047.4 ± 3.237.4	12.730.8 ± 7.332.3	0.004^{f}
	p-values	0.000^{f}	0.014^{f}	
POD 3	Low dosage (<0.05 µg)	3.140.1 ± 3.890.3	9.095 ± 6.109.4	0.045^{f}
	Normal doage (≥0.05)	8.015.2 ± 5.590.9	6.181	0.694
	p-values	0.000^{f}	1^{f}	

Note: POD: Post-operative day; AHF: Acute heart failure.; f. Mann-Withney U test.

Discussion

NT-proBNP reflected the grade of heart failure [19] and proved to be useful indicator for evaluating heart failure [16] In cardiac surgery, it pointed out as independent indicator to predict postoperative outcomes [20]. Compared with other indicators, it seems to be equal to euroSCORE but superior than ejection fraction [21]. It was used in various types of cardiac surgery such as percutaneous coronary intervention [22], surgery for aortic stenosis.[23], and CABG [11]. As the role of prognosis in CABG patients, NT-proBNP in combined with EuroSCORE II provided better prognosis accuracy with AUC = 0.93 and the cut-off point of NT-proBNP level was 1028 pg/ml [12]. When using it alone as an independent indicator to predict postoperative mortality, NT-proBNP also showed as valuable factor with HR = 2.02 and the cut-off point was 2,000 pg/ml [24]. To maximize the accuracy of NT-proBNP level, the cofounders that affected it must be eliminated. In general, factor affecting systolic function such as valve disease that can be elevated NT-proBNP level through elevating filling pressure of left ventricle [6]. Patients with heart valve abnormality (aortic or mitral stenosis) often had higher pre-operative levels than coronary diseases [25]. In our study, there was no patient with concomitant valve disease that reduced the risk of bias. The other important element affecting NT-ProBNP level was renal function. The relation between them was associated inversely [26] with increasing NT-proBNP level as decreasing eGFR [27]. Thus, in our study we excluded patients with renal function insufficiency to reduce the bias of NT-proBNP level.

NT-proBNP had shown evidence as a predictor of prognosis but what collecting time was better to predict also remained unknown [28]. One of the most advantages in our study was serial measurements of the NT-ProBNP that help to optimize the cut off value for specific circumstances. Using single NT-proBNP level measured before surgery to predict both severe circulatory failure and mortality in hospital after surgery [11]. Although preoperative measurement was independently predictive of postoperative outcome [29], [30], clinical assessment combined with biomarker tests also showed more useful value [7], [31]. However, natriuretic peptides were not included in post-operation follow-up. To further understanding, evaluating NT-proBNP in this period was needed. It was more valuable in prediction of mortality when using serial measurements within 12 hours [32]. It showed as strong predictors for both short-term and long-term prognosis [33].

When acute heart failure develops, NT-proBNP also increases and vice versa. That is why we used serum NT-proBNP level as an indicator of follow-up treatment in this study. It had been proved superior to standard care in guiding heart failure treatment with cost-effective, improving quality of life, and reversing ventricular remodeling [34]. Single NT-proBNP measurements can provide a diagnostic index, but it is unreasonable for treatment because of disease changing rapidly and need to use medical therapy to stabilize individual patients directly. Serial NT-proBNP measurements may provide intraindividual variation of NT-proBNP that reflects the real condition of patients. In our study, we used day by day measurements to follow continuously.The exact interpretation will lead to set up suitable treatment strategies. It can predict predicts adverse events during follow-up [35] and from that individually optimizing medical therapy for each patient [18]. In our study, level of NT-proBNP in AHF group was statistically significant compared to the without AHF group almost at POD 1 and POD 2 when analyzed by the doses of dobutamine, noradrenaline, and adrenaline (both low doses and normal doses). The dose of inotrope drugs was in line with NT-proBNP level. These results provide a valuable indicator in intensive management after CABG.

In conclusion, serial measurement of NT-proBNP level provides useful prognostic and follow-up treatment information in acute heart failure after CABG surgery.

Ethical approval

This study is approved by the ethics committee of 108 Military Central Hospital.

Informed consent

The consent and commitment were signed by the patients in the study

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