CARDIAC STRESS MARKER NT-proBNP AS AN INDICATOR OF CHANGES IN CARDIAC FUNCTION POST PERCUTANEOUS CORONARY INTERVENTION

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ABSTRAK

NT-proBNP adalah fragmen amino terminal dari prohormon BNP yang dilepaskan ketika terjadi peregangan dinding jantung akibat kelebihan volume. Peningkatan NT-proBNP terkait dengan keparahan gagal jantung dan fraksi ejeksi ventrikel kiri. PCI dapat memperbaiki fungsi jantung pasien dengan PJK yang menunjukkan peningkatan fraksi ejeksi. Tujuan dari penelitian ini untuk menganalisis perubahan tingkat NT-pro-BNP dan fraksi ejeksi, dan menganalisis hubungan antara fraksi ejeksi sebagai indikator fungsi jantung dan NT-proBNP sebagai penanda stres jantung pada pasien PJK yang menjalani PCI. Sebuah penelitian observasional cross-sectional dilakukan untuk menganalisis kadar NT-pro-BNP dan fraksi ejeksi pada pasien dengan penyakit jantung koroner yang menjalani PCI. Kriteria inklusi semua pasien berusia ≥ 30 tahun dengan diagnosis PJK dan menjalani PCI. Kriteria eksklusi semua pasien yang memiliki riwayat stenosis aorta, regurgitasi aorta, hipertensi pulmonal, kardiomiopati hipertrofik, dan penyakit ginjal. Sampel diambil dengan metode consecutive sampling. Kadar NT-proBNP diukur sebelum dan 96 jam setelah PCI. Pada pra-PCI, kadar NT-proBNP adalah 909,66 ± 1 360,56 pg/mL sedangkan fraksi ejeksi adalah 56,40 ± 11,68% dan pada pos-PCI, kadar NT-proBNP adalah 791,22 ± 1 234,67 pg/mL sementara fraksi ejeksi adalah 61,33 ± 11,09%. Terdapat hubungan antara kadar NT-proBNP dan fraksi ejeksi (r = -0,572, p = 0,001), menunjukkan bahwa setiap penurunan kadar NT-pro-BNP terjadi perubahan fungsi jantung terkait dengan peningkatan fraksi ejeksi, dan sebaliknya. Simpulan, kadar NT-proBNP maupun fraksi ejeksi tidak berbeda bermakna. Korelasi yang signifikan antara kadar NT-proBNP dan fraksi ejeksi dapat digunakan memprediksi gagal jantung pasca PCI. ***(FMI 2015;51:16-21)***

Kata kunci:*NT-proBNP, ejection fraction, coronary heart disease, percutaneous coronary intervention, cardiac biomarker*

ABSTRACT

NT-proBNP is an amino terminal fragment of prohormone BNP released when there is cardiac wall stretch due to volume overload. The increase in NT-proBNP associated with the severity of heart failure and left ventricular ejection fraction. PCI can be improved cardiac function of patients with CHD who indicated an increase in ejection fraction. The purpose of this study to analyze changes in NT-proBNP levels and ejection fraction, and analyze correlation between ejection fraction as an indicator of cardiac function and NT-proBNP as cardiac stress marker in CHD patients undergoing PCI. An observational cross sectional study was conducted to analyze NT-proBNP levels and ejection fraction in patients with coronary heart disease who underwent PCI. The inclusion criteria were all patients aged ≥ 30 years with a diagnosis of CHD and underwent PCI. Exclusion criteria were all patients who had history of aortic stenosis, aortic regurgitation, pulmonary hypertension, hypertrophic cardiomyopathy, and kidney disease. The sample was drawn with consecutive sampling method. NT-proBNP levels was measured before and 96 hours after PCI. In pre-PCI, NT-proBNP levels was (909.66 ± 1360.56) pg/mL while ejection fraction was (56.40 ± 11.68) % and in post -PCI, NT-proBNP levels was (791.22 ± 1234.67) pg/mL while ejection fraction was (61.33 ± 11.09)%. There was a correlation between NT-proBNP levels and ejection fraction (r = -0.572, p = 0.001), showed that every decrease in the levels of NT-proBNP indicates a change in heart function associated with an increase in ejection fraction, and vice versa. In conclusions, there was significant difference neither in NT-proBNP levels nor in ejection fraction. The significant correlation between NT-proBNP levels and ejection fraction can be used for prediction of heart failure post PCI. ***(FMI 2015;51:16-21)***

Keywords: *NT-proBNP, ejection fraction, coronary heart disease, percutaneous coronary intervention, cardiac biomarker*

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INTRODUCTION

Coronary heart disease (CHD) is a disorder of the coronary arteries caused by progressive atherosclerosis (Libby 2008). Risk factors for CHD include major, minor, thrombogenic and inflammatory risk factors (Mackay & Mensah 2004, Fauci et al 2008). The process of atherosclerosis is triggered by the presence of endothelial dysfunction resulting in decreased production of NO, increased cyclooxygenase activity and

inflammation. Changes in vascular function, particularly the coronary arteries, can cause an imbalance of myocardial oxygen supply and demand resulting in myocardial ischemia and angina (Rosen & Gelfand 2009, Jackson 2011, Bonow et al 2012). The process of cardiac damage causes release of intracellular proteins and certain specific enzymes that can be used as a biomarker for assessing diagnosis and prognosis of cardiovascular disease. One of biomarker that increases when myocardial ischemia, myocardial stress and heart failure occurs, is natriuretic peptide. Natriuretic peptide include Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP)/N Terminal-pro Brain Natriuretic Peptide (NT-proBNP), and C-type Natriuretic Peptide (CNP) (McLean & Huang 2012).

NT-proBNP is an amino terminal fragment of prohormone BNP released when there is cardiac wall stretch due to volume overload (Potter et al 2006). The increase in NT-proBNP associated with the severity of heart failure and left ventricular ejection fraction (Seino et al 2004). Measurement of NT-proBNP levels higher than BNP because NT-proBNP as passively cleared from the circulation much longer than BNP (Kim & Januzzi Jr 2011). NT-proBNP is a better marker for the detection of heart failure than BNP because NT-proBNP has good stability in sampling and increased NT-proBNP is higher than BNP in heart failure (Seino et al 2004). NT-proBNP levels at 96 hours after PCI is a powerful predictor for the long-term prognosis (Buchner et al 2010).

Percutaneous Coronary Intervention (PCI) indicated in ischemic heart disease with one or more coronary stenosis diameter >50% that cause the clinical syndromes such as recurrent chest pain that is disturbing and can not be treated with anti angina, and the risks and benefits better than surgery bypass (Smith et al 2001, Baim 2010, Popma & Bhatt 2012). Other research has shown that there is a correlation between the ejection fraction with NT-proBNP as a cardiac stress marker. NT-proBNP has been widely used as a predictor of cardiac stress and heart failure (Januzzi et al 2006). Changes in NT-proBNP may be occured in CHD patients undergoing PCI so it can be used as an indicator of changes in cardiac function for prediction of restenosis and heart failure post PCI.

MATERIALS AND METHODS

This observational cross-sectional study is conducted for 4 months (August-November 2013). Population subject were patients with coronary heart disease who underwent PCI in Cardiology and Vascular Inpatient Installation in Dr. Soetomo Hospital. Patients were elected by consecutive sampling, we took every patient who fulfills the criteria. NT-proBNP levels was measured before and 96 hours after PCI. Inclusion criteria for this study were all patients aged ≥ 30 years with a diagnosis of CHD and underwent PCI who were willing to sign informed consent. While exclusion criteria includes patients who had history of aortic stenosis, aortic regurgitation, pulmonary hypertension, hypertrophic cardiomyopathy, and kidney disease.

Data Analysis and Statistics

For analyzing the alteration of ejection fraction and NT-proBNP levels between pre- and post- data, we used paired t-test for normal distribution and Wilcoxon test for the other one. While to correlate between ejection fraction and NT-proBNP levels, we used Pearson Product Moment if the distribution is normal and Rank Spearman if it is not normal. We used the differences between pre- and post- data as parameters.

RESULTS

Number of samples who fulfill inclusion criteria from August until November 2013 were 15 patients. Sample of study characteristics are shown in Table 1. Pre-data NT-proBNP was collected before patients underwent PCI and post-data NT-proBNP was collected 96 hours after PCI. While pre-data ejection fraction was collected a month before patients underwent PCI and post-data ejection fraction was collected a week after PCI. Statistical analysis used to compare between pre-data and post-data is Wilcoxon test for NT-proBNP levels and paired t-test for ejection fraction. The results of this test are shown in Table 2. There are significant change between pre- and post-data either for NT-proBNP levels ($p = 0.001$) or ejection fraction ($p = 0.000$).

Table 1. Sample of Study Characteristics

Patients Characteristics	Number of Patients	% or mean ± SD
Gender		
Male	12	80
Female	3	20
Age (years)		55.27 ± 7.5
< 50	3	20
50 – 75	12	80
> 75	-	-
Risk Factors		
Diabetes Mellitus	5	33.3
Hypertension	8	53.3
Dyslipidemia	9	60
Smoking	11	73.3
Obesity	1	6.7
Family History	1	6.7

of CHD		
Stenosis Locations		
RCA	8	53.3
LAD	6	40
LCx	2	13.3

Table 2. Statistical Analysis between Pre- and Post- NT-proBNP and Ejection Fraction

Parameter	Range	Mean ± SD	p value
NT-proBNP	Pre (50-3913)	909.66 ± 1360.56	0.001
	Post (50-3567)	791.22 ± 1234.67	
Ejection Fraction	Pre (37-78)	56.40 ± 11.68	0.000
	Post (43-82)	61.33 ± 11.09	

The result of statistical test showed a correlation between NT-proBNP levels and ejection fraction (r = -0.572, p = 0.001). The correlation demonstrated that every decrease in the levels of NT-proBNP indicates a change in heart function associated with an increase in ejection fraction. The relationship between NT-proBNP levels and ejection fraction among subjects with CHD who underwent PCI is demonstrated in Figure 1.

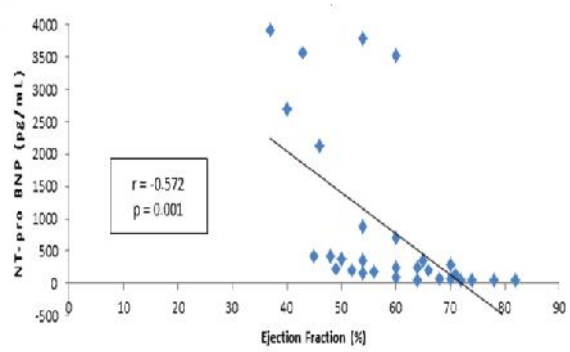

Figure 1. Relationship between NT-proBNP and Ejection Fraction

DISCUSSION

Demographic data found 12 male patients, 3 female patients, aged 40-80 years. The data shows smoking, dyslipidemia, hypertension, and diabetes mellitus as the major risk factors in atherosclerosis. Nicotine in cigarettes stimulates ganglionic receptors resulting in the release of adrenergic neurotransmitters that cause an increase in lipolysis, glycolysis, and heart rate. In addition, sympathetic nerve stimulation causes hypertension and adrenal medulla stimulation causes the release of epinephrine resulting in vasoconstriction (Lüllmann et al 2005).

In DM, decreased insulin sensitivity causes an increase in blood glucose and AGE's product resulting in dyslipidemia and decrease in NO, increase in ROS, DAG-PKC pathway activation resulting in desensitization of Ca2+ miofilamen (decrease cardiac contractility), activation of factors that cause fibrosis, and myocyte apoptosis. The process causes vascular damage, ventricular dysfunction, and cardiomyopathy (Picchi et al 2010, Hegab et al 2012). From the diagnosis, most patients are 2-3 occlusions with diameter of 70-100%, most locations in the RCA and LAD. The left coronary artery supplies 75-100% left ventricular mass. Occlusion will decrease blood flow most of the myocardium, resulting in high-risk LV dysfunction and arrhythmias (Chen et al 2004, Fajadet & Chieffo 2012).

Therefore, the patient will undergo PCI that is a choice for coronary revascularization than CABG. It's because PCI has several advantages compared to CABG, such the lower risk of death (< 0.5% vs < 1.5%), lower risk of myocardial infarction (2% vs 10%), length of stay 12-36 hours, and rare neurological complications (Boon et al 2006). Ejection fraction (EF) indicate left ventricular function. AHA criteria divide into hyper-dinamic (> 70%), normal (50-70%), mild dysfunction (40-49%), moderate dysfunction (30-39%), and severe dysfunction (< 30%) (Hendel et al 2009). There were 5 patients had an EF pre-PCI < 50%. Based on the results of the study, there was an increase of EF (56.40 ± 11.68)% pre-PCI into (61.33 ± 11.09)% post PCI. Though there were 3 patients still had an EF < 50% because they have many risk factors, especially smoking and dyslipidemia that can damage the heart muscle, causing myocardial stiffness caused left ventricular dysfunction (Mackay & Mensah 2004, Deedwania 2011).

The process of inflammation, endothelial damage and plaque formation resulting in myocardial ischemia, cardiac necrosis, and cardiac damage that causes the release of intracellular proteins and certain specific enzymes, such as NT-proBNP (McLean & Huang 2012). NT-proBNP is a better marker than BNP because it has a longer half-life (120 minutes vs 20 minutes), more stable, and the measurement of NT-proBNP levels higher than BNP (McMurray et al 2012, Kim & Januzzi Jr 2011). NT-proBNP levels at 24 hours post PCI will be increased, then decreased significantly at 96 hours after successful reperfusion (Buchner et al 2010). NT-proBNP levels have a very wide range because influenced by age, therefore we use category optimal cut-point of 450 pg/mL for age < 50 years, 900 pg/mL for ages 50-75 years, 1800 pg/mL for age > 75 years (Januzzi et al 2006). Based on the results of the study, there were 3 patients with NT-proBNP levels (3536

pg/mL, 3567 pg/mL, 2127 pg/mL) exceeds the optimal cut-point (900 pg/mL), indicating a tendency to a heart attack. Patient's anamnesis states a recent heart attack with risk factors of dyslipidemia and smoking, never examine their health as well as never take medication.

There are significant change either for NT-proBNP levels ($p = 0.001$) between NT-proBNP pre (909.66 ± 1360.56) and NT-proBNP post (791.22 ± 1234.67), or ejection fraction ($p = 0.000$) betwen EF pre (56.40 ± 11.68) and EF post (61.33 ± 11.09). Range of NT-proBNP pre overlapping with NT-proBNP post because NT-proBNP was strongly influenced by age, ventricular wall stress, ischemia, arrhythmias, fibrosis, ventricular hypertrophy and endothelial dysfunction (Januzzi et al 2006, Sahu et al 2010, Magnusson et al 2004). The result of statistical test showed a correlation between NT-proBNP levels and ejection fraction ($r = -0.572$, $p = 0.001$). Thecorrelation demonstrated that every decrease in the levels of NT-proBNP indicates a change in heart function associated with an increase in ejection fraction, and vice versa.

Correlation EF and NT-proBNP pre- and post-PCI showed NT-proBNP can be used as a predictor of prognosis of acute heart failure post PCI. Based on the study, predictors of mortality from acute heart failure include NT-proBNP, age, creatinine, hemoglobin, and paroxysmal nocturnal dyspnoea. Optimal NT-proBNP cut-point as a predictor of 76 days mortality due to acute heart failure was > 5180 pg/mL (Januzzi et al 2006). Pre-PCI therapy used in Dr. Soetomo General Hospital are antiplatelet ASA 1x100 mg and Clopidogrel 1 x 75 mg LD 300 mg (SKFT RSUD Dr. Soetomo 2010). ASA inhibits platelet aggregation through selective blockade of cyclooxygenase, thus preventing the synthesis of Thromboxane A2 (Lüllmann et al 2005). Clopidogrel is a prodrug that is activated by CYP2C19, works by blocking the ADP receptor P2Y12 subtype that can activate platelets. Onset of action of Clopidogrel is slow, thus requiring a loading dose of 600 mg or 300 mg for accelerating effects (Wallentin 2009).

Research on the Asian race, Clopidogrel 600 mg no better than 300 mg due to polymorphism of CYP2C19 RM genotype (Caucasian 20-30%, East Asian 50-65%) which decreases the pharmacodynamic response. Approximately 85% of the prodrug is converted to inactive metabolites, resulting in small change in the activity of CYP enzymes affects the formation of active metabolites. Platelet inhibition by Clopidogrel is dose dependent but not dose proportional, therefore LD 300 mg on the Asian race is sufficient therapeutic dose (Song et al 2012, Varenhorst et al 2009, Wallentin 2009). Some patients known to regularly taking medication such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statins. Drug effects on cardiomyocyte secretion levels depending on the amount of the complex interaction of several signals that alter ventricular stress. The induction signal is affected by stimulus from other sources including Renin-Angiotensin-Aldosterone system, sympathetic nervous system (α_1-agonist stimulation and β-agonists inhibition), thyroid hormone, vasopressin, prostaglandins, hypoxia/ ischemia and cytokines (Troughton et al 2007). Decreased levels of BNP/NT-proBNP with therapy may be associated with reduced risk and improved prognosis resulting in better clinical outcomes (Troughton & Nicholls 2011, Antonopoulos et al 2012).

CONCLUSION

NT-proBNP as a cardiac stress marker correlates with ejection fraction as an indicator of changes in cardiac function. Therefore, NT-proBNP can be used for prediction of heart failure post PCI.

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