CORRELATION BETWEEN N-TERMINAL PRO-BRAIN NATRIURETIC PEPTIDE LEVEL WITH DYASTOLICFUNCTION ECHOCARDIOGRAPHY PARAMETER IN ACUTE CORONARY SYNDROME

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ABSTRAK

Sindrom koroner akut adalah salah satu penyebab paling umum kematian. Ekokardiografi untuk mengevaluasi fungsi ventrikel kiri (LV) telah menjadi komponen penting dalam penilaian risiko. Pengunaan beberapa variabel biokimia juga telah diakui dan N-Terminal Pro-Brain Natriuretic Peptida (NT-proBNP) telah terbukti menjadi penanda prognostik penting yang dihasilkan sebagai respon dari stres dinding dan peregangan miosit ventrikel. Peningkatan NT-proBNP pada kondisi Sindroma Koroner Akut berasosiasi dengan prognosis yang buruk termasuk peningkatan mortalitas, timbulnya gagal jantung kongestif, dan kejadian iskemia berulang. Penelitian ini Bertujuan Untuk menganalisa hubungan antara konsentrasi N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) dan parameter ekokardiografi fungsi diastolik ventrikel kiri pada Sindroma Koroner Akut, dengan cara Mengukur kadar plasma NTproBNP penderita Sindroma Koroner Akut di IRD dan ICCU RSUD Dr. Soetomo. Konsentrasi NT-proBNP diukur menggunakan kit RELIA TM Immunoassay Diagnostic Instrument (SSJ-2) dengan metode Elisa, yang diukur pada jam pertama dan ke-6 setelah masuk rumah sakit dan ekokardiografi dilakukan untuk mengevaluasi fungsi ventrikel kiri pada saat penderita masuk. Terdapat 34 subyek penelitian yang terdiri dari wanita dan pria dengan rata – rata usia adalah 35-79 tahun. Nilai rata-rata NT-proBNP pada jam pertama, ke-6 dan konsentrasi puncak adalah 2040,3062 ± 4169,89471 pg/ml dan 2683,3376 ± 4190,66055 pg/ml. Nilai rata-rata E/A adalah 0,8676 ± 0,26825 dan DT 238,24 ± 39,134 ms. Tidak terdapat korelasi antara konsentrasi NT-proBNP baik pada jam pertama dan ke-6 dengan E/A. Terdapat korelasi antara konsentrasi plasma NT-proBNP dan DT fungsi diastolik ventrikel kiri pada ekokardiografi sindrom koroner akut.(FMI 2014;50:25-29)

Kata Kunci: Sindroma Koroner Akut, NT-proBNP, Ekokardiografi

ABSTRACT

Acute coronary syndromes is one of the most common cause of death. Echocardiography for the evaluation of left ventricular (LV) function has become an important component in risk assessment. the usefulness of various biochemical variables has been recognized and N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) has been proven to be an important prognostic marker and released as a respons of wall stress and myocyte stretch. Elevated NT-proBNP concentrations at admission in the setting of ACS are associated with poor prognosis, including increased mortality, \development of CHF, and recurrent ischemic events. This study Aim For analyze correlation between serum level of NT-proBNP and echocardiography parameters left ventricle diastolic function in Acute Coronary Syndrome. by means we measured plasma level of NTproBNP 34 Acute Coronary Syndrome patients in Emergency Departement and ICCU Dr.Soetomo Hospital. RELIA TM Immunoassay Diagnostic Instrument (SSJ-2) kit was used to measured NT-proBNP concentrations with ELISA method, on 1 and 6 hours after admission and echocardiography was perform on admission to determine LV dysfunction. There were 34 subject, women and men and mean age was 35-79 years old. The mean of peak NT-proBNP, 1 and 6 hours after admission consecutively were 2040,3062 ± 4169,89471 pg/ml and 2683,3376 ± 4190,66055 pg/ml. The mean peak E/A 0,8676 ± 0,26825 and DT 238,24 ± 39,134. There was no correlation between NTproBNP concentration on 1 and 6 hours after admision and peak E/A. There was a correlation between plasma NT-proBNP level and DT on echocardiography in acute coronary syndromes(FMI 2014;50:25-29)

Keywords: Acute Coronary Syndrome, NT-proBNP, echocardiography

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INTRODUCTION

Acute coronary syndrome (ACS) is a collection of symptoms and signs caused by an imbalance between myocardial oxygen supply and demands. The reduction in coronary blood flow cause myocardial ischemia, which can lead to symptoms of chest pain. Most of the Acute coronary syndrome (ACS) is an acute manifestation of coronary artery atheroma plaques rupture. Oxygen supply that stopped for about 20 minutes can cause myocardial necrosis (myocardial infarction/IM). ACS is a major cause of morbidity and

mortality in developed countries and a major cause of death in western country. Ministry of Health of the Republic Indonesia in 2008 showed that the vascular systemic diseases were the highest cause 11.06% of all deaths in hospital (Yeh et al 2010)

Natriuretic peptide is released from the heart in conditions of increased pressure and volume in the ventricle. Over the last decade, N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) has been proposed as a useful marker for determination of acute cardiac left ventricular dysfunction, chronic and severity of left ventricular systolic dysfunction. Brain Natriuretic Peptide is basic used to diagnose congestive heart failure, but also known to be elevated in conditions of Acute Coronary Syndrome. Some recent evidence suggests that BNP and NT pro-BNP can be used to establish the diagnosis and determine the prognosis of patients with myocardial infarction. BNP is a neurohormone synthesized 32 amino acids in the form of pre-proBNP, which is first split into pro-BNP, and then became active BNP and the inactive fragment NT-proBNP (Fox 2000, Kumar & Cannon 2009).

Echocardiography is a standard method that has been widely used to assess left ventricular dysfunction and indirectly measure left ventricular filling pressure. This method is very useful for understanding the mechanism of the heart due to acute coronary syndrome, help determine the etiology and can provide information on the progress of therapy and prognosis (Bassand et al 2007, Horowitz et al 1982). Echocardiography is also useful for determining diastolic dysfunction in patients with acute coronary syndrome. Severity of diastolic dysfunction was assessed by Doppler echocardiography. On this basis the researchers wanted to know whether there is a relationship between NTproBNP levels with the severity of diastolic dysfunction in patients with acute coronary syndrome (Falk 2006, Hansson 2005, Sabia et al 1991).

MATERIAL AND METHODS

This is a observasional study of 34 consecutive patients of acute coronary syndromes admitted to the coronary care unit Dr Soetomo General Hospital. These patients had no prior history of myocardial infarction and heart failure. All patients who met the inclusion criteria of each sample performed blood sampling for NTproBNP and echocardiography examination was performed when he first entered in emergency room. Blood samples were taken from a peripheral vein as much as 3 cc, put into EDTA tubes and rocked a few times, then centrifuged for 12 minutes at 3000 rpm. As soon as the plasma is taken from the specimens included in the

sample cup which has a name, study number, date and time of blood sampling and then stored in a temperature -20 degrees Celsius to await examination of NT pro-BNP levels in the laboratory. NTproBNP values measured using the ELISA kit RELIA TM Immunoassay Diagnostic Instrument (SSJ-2). Echocardiography examination was performed when the blood sample had been taken using GE Vivit 7. Patients were evaluated in 2-D, M-mode, color mapping, and Doppler echocardiography. The variables evaluated included left ventricular diastolic function by evaluating the Doppler signals of transmitral blood flow and calculate the value of E/A and DT.

RESULTS

This study was carried out on 34 patients suffering from acute coronary syndromes consisting of 17 patients suffering from acute myocardial infarction, 3 patient suffering from non-ST elevation myocardial infarction and 14 patients suffering from unstable angina during the period May 2013 to July 2013. This study also observed, patients with acute coronary syndrome are categorized by Killip classification that consists of a group of patients with acute coronary syndrome with Killip I through IV Killip. Groups of patients with Killip I counted 23 patients (67%), Killip II 6 patients (18%), Killip III were 3 patients (9%) and Killip IV 2 patients (6%). The mean examination ejection fraction by echocardiography include Teich $55.71 \pm 10.053\%$, mitral inflow E/A ratio of 0.8676 ± 0.26825 and DT was 238.24 ± 39.134 ms.

All parameters echocardiography, after the test data normality test showed that the data are not normally distributed with: p value Kolmogorov Smirnov or Shapiro Wilks for E/A of $0.000 <0.1$, p value Kolmogorov Smirnov or Shapiro Wilks for DT of $0.000 <0.1$ and p value Kolmogorov Smirnov or Shapiro Wilks for NTproBNP of $0.000 <0.1$. Because the data are not normally distributed then to determine the relationship between NTproBNP with E/A and DT a Spearman correlation analysis was performed.

The Spearman correlations analysis show there is no correlation between NTproBNP with E/A with p-value 0.161, but there is a strong correlation between NTproBNP with DT with p-value of 0.009 and Spearman's rho correlation coefficient of -0.439. Marked negative (-) correlation coefficient indicates that the relationship is not unidirectional. Thus, if the value of NTproBNP is high than the DT value is low. From the statistics on Kruskal Wallis Test show there is a correlation between the value of NTproBNP and category diastolic function with p-value 0.000. Figure 1

shows the increased NTproBNP in the group category pseudonormal diastolic function than those in the category abnormal relaxation diastolic function.

Table 1. The baseline characteristic of patients suffering from ACS

|	Total	Infark STEMI/NSTEMI	UA
Age	: 55.76 $\pm$ 11.322	52.25 $\pm$ 11.346	60.79 $\pm$ 9.545
Male	: 19 (55.9%)	12 (35.3%)	7 (20.6%)
Female	: 15 (44.1%)	8 (23.5%)	7 (20.6%)
Smoking	: 15 (44.1%)	10 (29.4%)	5 (14.7%)
Hypertension	: 23 (67.6%)	15 (44.1%)	8 (23.5%)
Diabetes	: 11 (32.4%)	8 (23.5%)	3 (8.8%)
UA	14 (41.2%)		
NSTEMI	3(8.8%)		
STEMI	17(50%)		
Killip 1	22 (64.7%)		
Killip 2	6 (17.6%)		
Killip 3	3 (8.8%)		
Killip 4	2 (5.9%)		
Systolic	: 124.88$\pm$24.070	122 $\pm$ 20.700	128.36 $\pm$28.678
Diastolic	: 76.12 $\pm$ 10.887	74.50 $\pm$ 11.910	78.43$\pm$ 9.154
CKMB 1 h	: 99.4206 $\pm$ 145.84275	149.21 $\pm$ 174.39	28.2929$\pm$16.84721
CKMB 6 h	: 120.4147 $\pm$ 156.01615	190.86 $\pm$ 171.95	19.7786$\pm$ 5.94270
Troponin T 1 h	: 0.4424 $\pm$ 0 .61906	0.7510 $\pm$ 0.64967	0.0014 $\pm$0.00363
Troponin T 6 h	: 0.7168 $\pm$ 0. 81502	1.2175 $\pm$ 0.71604	0.0014$\pm$ 0.00363
LDH	: 596.74 $\pm$ 457.433	792.05 $\pm$ 509.564	317.71 $\pm$95.567
Total cholesterol	: 193.50 $\pm$ 41.735	193.55 $\pm$ 52.171	193.57 $\pm$21.063
LDL	: 137.71 $\pm$ 35.732	130.85 $\pm$ 38.5	147.50 $\pm$29.984
HDL	: 33.32 $\pm$ 9.344	30.40 $\pm$ 9.528	37.50 $\pm$7.552
Triglyceride	: 179.79 $\pm$ 48.462	166.05 $\pm$ 45.475	199.43 $\pm$47.260
EF	: 55.71$\pm$ 10.053	52.95$\pm$ 10.49047	59.6429$\pm$ 8.20513
E'	: 0.0659 $\pm$ 0.00657	0.0655$\pm$ 0.00759	0.0664 $\pm$0.00497
E/E'	: 8.2193 $\pm$ 1.49864	8.6886 $\pm$1.71585	7.5489 $\pm$0.75847
A	: 0.7326 $\pm$ 0.62598	0.8341$\pm$ 0.67364	0.4147 $\pm$0.48501
E/A	: 0.8676 $\pm$ 0.26825	0.9835 $\pm$0.35978	0.8629 $\pm$0.20559
DT	: 238.24 $\pm$ 39.134	224.65$\pm$ 41.89188	257.64 $\pm$25.379
NTproBNP	:2040.3062$\pm$4169.89471	3182.1$\pm$5163.07232	409.22$\pm$554.50214
NTproBNP 6 h	:2683.3376$\pm$4190.66055	4142.1$\pm$4971.40194	600.10$\pm$712.53186
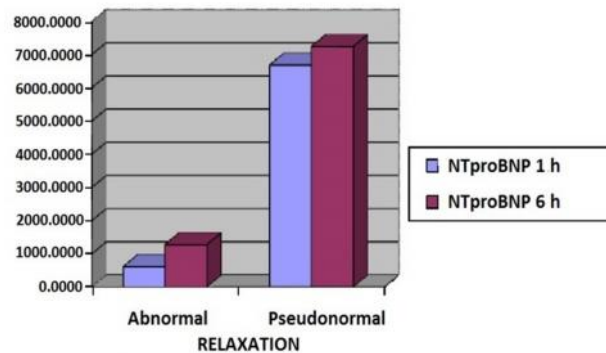
Figure 1. NTproBNP levels based on category diastolic function

DISCUSSIONS

This study was carried on 34 patients suffering from acute coronary syndromes in all clinical spectrum including acute ST elevation myocardial infarction, acute non ST elevation myocardial infarction and unstable angina and there was no history of heart failure. Clinical evaluation on patients suffering from acute coronary syndromes is extremely important to determine complication and prognosis. Early finding of left ventricular diastolic dysfunction due to acute coronary syndromes is useful to give the optimum therapy and to prevent heart failure that ultimately worsens the coronary perfusion (Libby et al 2009). This study analyzes whether there is a relationship between plasma NTproBNP levels with echocardiography parameters left ventricular diastolic function of E/A and DT in acute coronary syndrome patients.

NTproBNP has been used extensively as a marker for cardiovascular diseases. Especially in heart failure, which is used for diagnosis, prognosis and risk stratification or treatment monitoring (Tabas et al 2007, Thim et al 2008). In the acute coronary syndromes and stable coronary heart disease, NTproBNP has reported as a very strong prognostic indicator. The latest report also showed that the left ventricular diastolic function contributes importantly to the NTproBNP plasma levels and thus can be used to diagnose diastolic heart failure (Kramer et al 2010, Shah 2003). B-type natriuretic peptide is synthesized as a prohormone (proBNP) which consists of 108 amino acids. Once released into the circulation, will be cleaved by serine proteinase furin to the 32-amino acid biologically active BNP, which is a C-terminal fragment and a 76-amino acid N-terminal inactive (NT) proBNP (Virmani et al 2006, Davies 2000, Giroud et al 1992). Both molecules are synthesized sequentially and can be detected in the blood. Although the main stimulus for increased BNP and NT-proBNP is myocardial wall stress, several other factors also contribute to their regulation. Myocardial ischemia and neurohormone modulation with other endocrine and cytokines are also important (Libby et al 2002, Anand et al 2008). Clinically, it has been shown consistently that NTproBNP related to gender, with higher valuesin women, age, with higher valuesin the elderly, and obese, with a lower value on the subject of overweight and obesity (Clerico & Emdin 2004, Mair 2008). In patients with renal insufficiency, levels of both BNP and NTproBNP value is increased and varied in most patients without symptoms. Many research data to date indicate that BNP and NT-proBNP are both equally useful as a diagnostic and prognostic marker in clinical setting (Nishikimi et al 2006, de Lemos et al 2003, Munagala et al 2004). The secretion of NTproBNP by infarction due to myocardial wall stress on the heart can end with diastolic left ventricular dysfunction. The examination NTproBNP may be accepted as a rapid and reliable for diagnosing asymptomatic left ventricular diastolic dysfunction (Lam et al 2007, Martinez-Rumayor et al 2008). Left ventricular diastolic dysfunction can be assess by Doppler mitral inflow E/A and DT on ekokardiografi (Karaca et al 2007). Correlation is found between NTproBNP and echocardiography parameters E/A on univariate analysis, but did not correlate in multivariate analysts in patients with acute coronary syndrome (van Kimmenade et al 2009, Belenky et al 2004, Ordonez-Llanos et al 2008). In this study there were no significant differences in levels of NTproBNP and echocardiography parameters E/A in patients with acute coronary syndrome. However NTproBNP levels strongly. correlated with echocardiography parameters DT, where the higher value of NTproBNP the lower DT value will in patients with acute coronary syndrome.

CONCLUSIONS

Plasma NTproBNP level can be used to detect the presence of diastolic LV dysfunction on echocardiography in early events of acute coronary syndromes. In patients with acute coronary syndrome NTproBNP plasma levels increased with severity of left ventricular dysfunction as measured by the parameter E/A ratio and DT.

ACKNOWLEDGMENT

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