ANALYSIS OF CHANGES IN THE SERUM LEVEL NT-proBNP AFTER ACE INHIBITORS THERAPY IN PATIENTS WITH HEART FAILURE

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ABSTRAK

BNP utamanya disekresi oleh ventrikel jantung sebagai respon peregangan atau tekanan dinding ventrikel kiri yang terjadi pada pasien gagal jantung. Peningkatan kadar NT-proBNP berhubungan dengan derajat keparahan gagal jantung dan ejeksi fraksi ventrikel kiri. Beberapa penelitian klinis membuktikan modulasi neurohormonal pada sistem RAAS menurunkan nilai NT-proBNP dan memberikan hasil yang baik. Pengeblokan RAAS dilakukan dengan menggunakan terapi obat salah satunya ACE inhibitor, penurunan kadar NT-pro BNP menunjukkan respon terhadap terapi termasuk terapi ACE inhibitor. Mengkaji perubahan kadar NT-pro BNP baseline dan setelah 2 bulan sesudah pemberian terapi ACE-inhibitor pada pasien gagal jantung dan monitoring serum kreatinin.Ini merupakan penelitian observasional prospektif non random pada pasien gagal jantung dengan kriteria inklusi pria atau wanita usia 21-75 th, didiagnosis NYHA kelas II-III, mendapatkan terapi ACE inhibitor maksimal 3 bulan sebelumnya ditambah terapi lain tanpa ARB atau beta bloker. Serum NT-proBNP dan kreatinin dibandingkan pada saat pre terapi dan setelah 2 bulan terapi menggunakan ACE inhibitor. Penelitian ini dilakukan di poliklinik jantung RSUD dr. Soetomo Surabaya. Selama bulan Agustus-November 2015, 13 pasien masuk dalam kriteria inklusi, baseline NT-proBNP 2166,92±1236,73 pg/mL, dan serum kreatinin 1,023±0,601 mg/dL. Evaluasi 2 bulan terdapat perbedaan bermakna antara pre dan post terapi nilai NT-proBNP 1508,23±651 pg/mL (p=0,025; p<0,05), serum kreatinin 0,951±0,0365 mg/dL (p=0,111; p>0,05). Pada penelitian ini prosentase penurunan NT_proBNP sebesar 26,7%, sedangkan satu pasien mengalami kenaikan NT-proBNP sebesar 67,8%. ACE inhibitor memberikan manfaat terhadap hambatan neurohormonal pada pasien dengan gagal jantung. Apabila diperlukan NT-pro BNP dapat dipilih sebagai marker pendukung prognosis dan digunakan untuk monitoring terapi yang diberikan terhadap pasien gagal jantung, terutama pada penelitian ini adalah ACE inhibitor. ***(FMI 2016;52:193-197)***

Kata kunci: *Peptida natriuretik, NT-proBNP, gagal jantung, angiotensin-converting enzyme inhibitors*

ABSTRACT

BNP secreted by left ventricle as response to wall stress in patient with heart failure. Elevated concentration of NT-pro-BNP correlate with severity of heart failure across all stages of the condition and left ventricle ejection fraction in patient. Several clinical trials have demonstrated that neurohormonal modulation on the RAAS decreases NT-proBNP level and results in favorable outcomes. One of the drug used for blocked RAAS system is ACE inhibitor, decrease of NT-proBNP level show response to therapy include therapy with ACE inhibitors. To analize changes in the levels serum NT-proBNP levels after ace inhibitor therapy in patients with heart failure and monitoring creatinine serum. This study was a observational, prospective, non-randomized trial involving patient age 21-75 years, with NYHA class II-III HF, using ACE inhibitor therapy plus other therapy maximum 3 months before study without ARB or beta blocker. We compared serum NT-pro-BNP and creatinin serum parameters before and after two months treatment with ACE inhibitor. This study conducted in cardiovascular ambulatory patient dr. Soetomo hospital Surabaya. Between August-November 2015, 13 patient (38-63 years, 6 woman, 7 men) include in this study. The mean baseline level of NT-proBNP is 2166.92±1236.73 pg/ml, and creatinin serum 1.023±0.601 mg/dL. The NT -pro-BNP were significantly decreased after two months of treatment with ACE inhibitors 1508.23±651 pg/mL (p=0.025), there were no significant differences creatinin serum between two groups 0.951±0.0365 mg/dL (p=0.111). The results demonstrated the benefits of ACE inhibitor on the neurohormonal profile in patients with HF. If necessary we could measure NT-proBNP level to support prognosis data and monitoring effectivity therapy especially ACE inhibitor which had antiremodelling effect towards patients with HF. ***(FMI 2016;52:193-197)***

Keywords: *Natriuretic peptide; NT-proBNP; heart failure; angiotensin-converting enzyme inhibitors*

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INTRODUCTION

In the current pathophysiological model, heart failure is characterized by a constant stimulation of several neuro-hormonal systems, which are able to restore the cardiac output in early phases of the process, but become inefficient, harmful and responsible for the progression of the myocardial dysfunction in the long term. BNP (Brain Natriuretic Peptide) secreted by left ventricle as response to wall stress in patient with heart failure

(Localzo et al 2010). The plasma concentration of BNP and its fragmen N-terminal pro-brain natriuretic peptide (NT-pro-BNP) is a strong prognostic indicator for patients with heart failure (HF) across all stages of the condition. NT-proBNP is favourable to analysis because of longer half live and stability in sample (Mueller 2004).

Several clinical trials have demonstrated convincingly that neurohormonal modulation on the renin angiotensin aldosterone system (RAAS) decreases plasma NT-proBNP level and results in favorable outcomes. One of the drug used for blocked RAAS system is ACE inhibitor. ACE inhibitor reduce intravascular volume, cardiac filling pressure, prevent remodelling in long term and the consequences reduce level of NT-proBNP. Decrease of NT-proBNP level show response to therapy include therapy with ACE inhibitors (Tsutamoto et al 2008). Still limited data for the effect of ACE inhibitor for the changes of neurohormonal activity in patients with heart failure.The natriuretic peptides have been the most frequently recommended measurement, given their good correlation with the severity of ventricular dysfunction and the consistent methodology for their analyses (Kim & Januzzi 2011).

The primary objective of this study was to to analize changes in the levels plasma nt-probnp levels after ace inhibitor therapy in patients with heart failure. Second-arily, to monitoring creatinine serum in patient with ACE inhibitors therapy for two months observ-ation.

MATERIALS AND METHODS

This study was a prospective, non-randomized trial conducted in cardiovascular ambulatory patient dr. Soetomo hospital Surabaya involving patient with age 21-75 years with heart failure NYHA class II, using ACE inhibitor therapy plus standard therapy maximum 3 months before study without disease. ARB or beta blocker and willing to follow this study by signing informed cosent We compared plasma NT-pro-BNP and creatinine serum parameters before and after two months treatment with ACE inhibitor. Patient which has creatinine serum > 2 mg/dL and BMI > 30 kg/m2 were excluded from the study.

Blood sample collected from all patient at baseline and two months after received ACE inhibitors therapy in order to analyze serum NT-proBNP and creatinine serum. The blood collected for serum NT-proBNP measurement was centrifuged and kept at –freezer until the time of the measurement. The sample were storage at 2-8oC freezer. The concentration serum NT-proBNP was measured by IMMULITE® 1000 Turbo device. In this study we used human NT-proBNP CLIA kit from IMMULITE. We performed the analysis in laborat-orium clinical pathology, diagnostic center building dr. Soetomo hospital Surabaya. Descriptive analyses were performed to determine the demographic, characteristic patient, and profile Nt-proBP and creatinine serum at baseline and post therapy two months. Changes in level NT-proBNP was measured by SPSS software using paired t-test methods. A p value<0.05 was regarded as significant.

RESULT

During the study period, 15 consecutive patient with heart failure were screened for eligibility. Of these, 13 were eligible. Baseline characteristic on admission are shown in table 1. Mostly patient age was 55-74 years and included 7 man and 6 woman. The most common cuse of heart failure in patients are old miokard infark (46.2%), 2 patient had AF and PHT as complication. All patient had DCFC NYHA class II.

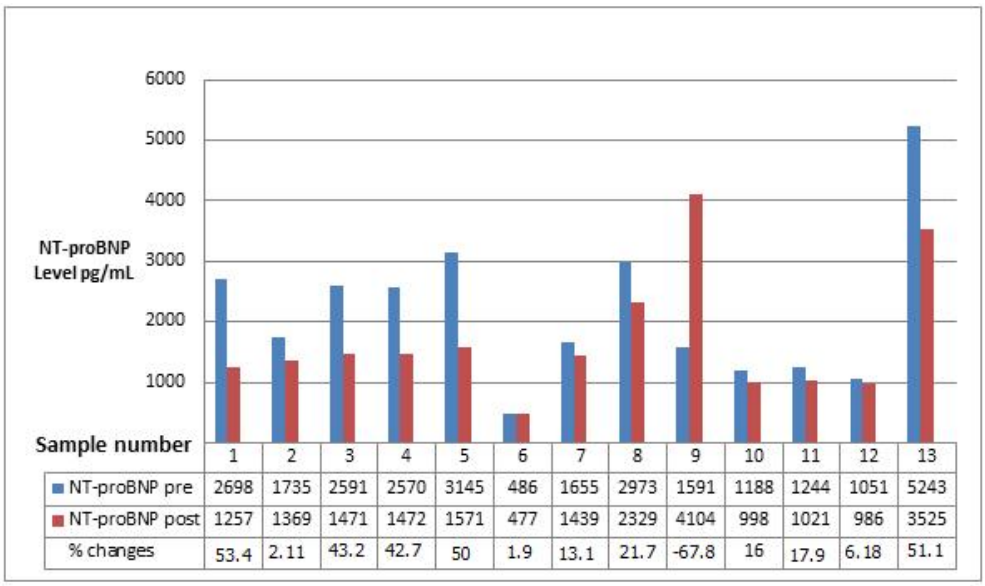
Table 1. Characteristics of subjects

Characteristic (N=13)		N (%)
Sex	Male	7 (54)
	Female	6 (46)
Age	35-56	6 (46.2)
	57-74	7 (53.8)
Diagnose	OMI	6 (46.2)
	Cardiomiopathy	3(23)
	VHD	4 (15.4)
Complication	PHT	2 (15.4)
	AF	15.4
ACE Inhibitor Therapy	Captopril 12.5 mg	1 (7.7)
	Lisinopril 2.5 mg	1 (7.7)
	Lisinopril 5 mg	3 (23.1)
	Ramipril 2.5 mg	5 (38.5)
	Ramipril 5 mg	3 (23.1)
Other Therapy	Furosemide	10 (76.9)
	Spironolactone	9 (69.2)
	Digoksin	9 (69.2)
	ASA	6 (46.1)
	ISDN	5 (38.5)
	Simvastatin	4 (30.8)
	Warfarin	4 (30.8)
	Clopidogrel	2 (15.4)
	Beraprost	2 (15.4)

* One patient may have one or more other other therapy

Serum NT-proBNP levels ranged from 486 to 5243 pg/ml at baseline. The average NT-proBNP value at baseline was 2166.92±1236,735 pg/ml. In the compar-isons between two months, we observed a mean reduc-tion by 803.5 pg/ml or 26.7% in relation to baseline. In post therapy two months serum NT-proBNP levels was 477 to 3525 pg/ml. The Average NT-proBNP levels at post two months 1508.23±651,094 pg/ml. Decreased of

NT-proBNP after two months occurs in 12 from 13 patient. One patient had increased Nt-proBNP levels from baseline. The levels of NT-proBNP baseline or pre therapy and post therapy of each patient shown in figure 1. There was significantly changes between NT-proBNP pre and after post two months therapy (p=0.025; figure 2) with ACE inhibitors in patients with heart failure. The secondary parameter was creatinin serum. There was no significantly diffrences between creatinine serum pre and post two months therapy with ACE inhibitors in patients with heart failure.



Sample number	1	2	3	4	5	6	7	8	9	10	11	12	13
NT-proBNP pre	2698	1735	2591	2570	3145	486	1655	2973	1591	1188	1244	1051	5243
NT-proBNP post	1257	1369	1471	1472	1571	477	1439	2329	4104	998	1021	986	3525
% changes	53.4	2.11	43.2	42.7	50	1.9	13.1	21.7	-67.8	16	17.9	6.18	51.1

Fig. 1. Serum NT-proBNP Each Patient Before and After two months ACE inhibitor Therapy

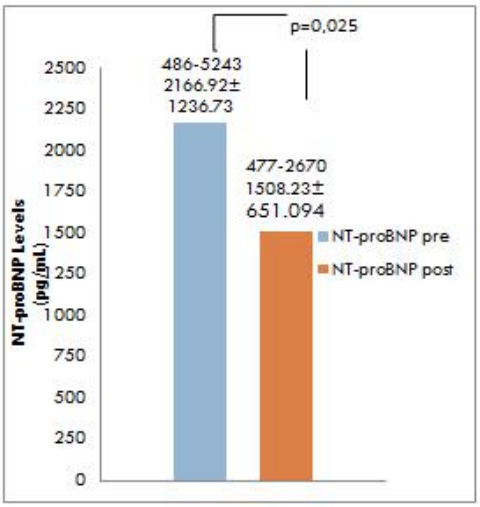


Fig. 2. Changes beetween NT-proBNP levels pre and post two months therapy

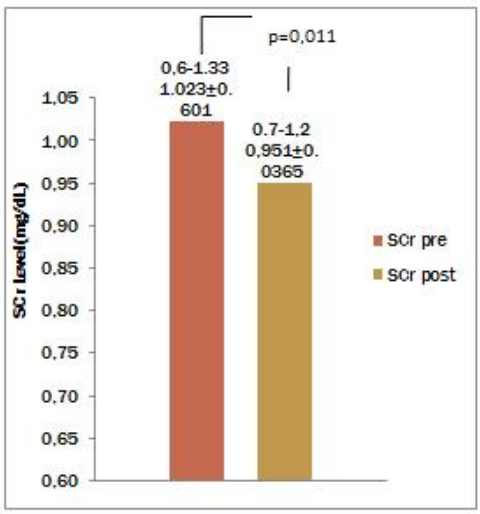


Fig. 3. Differences beetween creatinine serum pre and post two months therapy

Table 2. Category of NT-proBNP and GFR in this study

Category	Pre n(%)	Post n(%)	%Δ n(%)
NT-proBNP			
< 1000pg/ml	1(7.7)	3(23.1)	-
> 1000 pg/ml	12(92.3)	10(76.9)	-
> 25%	-	-	5(38.5)
< 25%	-	-	8(61.5)
GFR			
>60 ml/minutes	11(84.6)	12(92.3)	-
< 60 ml/minutes	2(15.4)	1(7.7)	-

The mean of % changes in NT-proBNP level were 26.7%. In the result of this study we divide NT-proBNP levels in patient into several category. First category was NT-proBNP below 1000 pg/ml and above 1000 pg/ml in pre and post therapy. Second category was changes of NT-proBNP levels at post more than 25% and changes less than < 25% (table 2). 1000 pg/ml was the cut off value for NT-proBNP in patient with chronic condition The result show 23.1% patient reached cut off target NT-proBNP levels. Changes NT-proBNP more than 25% (decrease or increase) show clinical significance. In this study 38.5% patient reached clinical significant changes. We also calculate the glomerulus filtration rate from creatinine serum of each patient with cocroft and gault methods and divide the GFR of patient into GFR above 60 ml/minute and below 60 ml/minute (table 2).

DISCUSSION

ACE inhibitors reduce intravascular plasma volume, ventricular filling pressure, and, consequently, NT-proBNP levels. In the treatment of HF, reductions in NT-proBNP concentrations, when detected by sequential analyses of the same patient, are correlated with improved symptoms, increased functional capacity, reduced rate of clinical endpoints and better prognosis. On the other hand, persistently elevated NT-proBNP levels despite treatment identify patients with worse prognosis (Neto 2008). Our result showed the beneficial effect of ACE inhibitor on reducing NT-proBNP levels as cardiac stress marker. By the end of two months, mean change of NT-proBNP level were 26.7% from baseline, with statistically significant reduction in all comparison. ACE inhibitor used in this study were ramipril, lisinopril and captopril and the dose use suited by patient condition. Patient tolerate well with therapy given, so during two months patient get stabil dose, no change or addition therapy such as ARB and beta bloker. In this study 9 patient use spironolacton which could reduce NT-proBNP level in long therm therapy (Tsutamoto 2001).

Cut off value below 1000 pg/ml in prior study showed significantly low risk of bad prognosis and outcome, whereas subjects with NT-proBNP concentrations above 1000 pg/ml showed high risk (Januzzi 2011). Beside cut off value, we could assess serial NT-proBNP levels from % change from baseline. Because of analytic imprecision and biological variation, NT-pro-BNP changes >25% from baseline correlate well with clinical course in follow-up of patients with heart failure (Morrow 2006). In this study, we found more patient not reached target cut off value < 1000 pg/ml and the decrease NT-proBNP levels still > 25% might be due observation time (two month) was not long enough. In several study before, the follow up time between 4-6 month.

In this study we found one patient experience increased NT-proBNP levels. Even though the patient looked stable, those with NT-proBNP increase >25% from baseline, associated with increased risk in hospitalisation and mortality. Consider for drug therapy intensification and/or careful reassessment of their medical programs irrespective of clinical status or perception of the presence of an optimal medical program (Januzzi 2011). Secondary parameter in this study was creatinin serum. Measurement the value of serum creatinine continuosly in patients receiving ACE inhibitor therapy is recommended to monitor the patient's renal function (de Boer & van Veldhuisen 2008). In this study, the SCr patient in pre and post therapy were in the normal range (0.6-1.3 mg/dl) and there is no significant difrences between SCr levels. Decrease of renal function < 40 ml/ minute could increase NT-proBNP levels because of decreased clearance (Srisawasdi et al 2010, Tsutamoto 2006). So we calculate each patient GFR, and the result patient in this study did not had severe renal failure that could affect NT-proBNP levels.

Study limitations. limitations of our study include that it was relatively small sample size. We couldn't exclude patient with spironolactone because of limited sample and that's might affect the result of this study. Vary between type and dose of ACE inhibitor used in this study and correlation with decreased of NT-proBNP levels need further study. A further study with a larger sample size, longer follow up time and controlled confounding condition suggested in order to get more representatif result.

CONCLUSION

The results in 13 patient demonstrated the benefits of ACE inhibitor on the neurohormonal profile in patients with HF. If necessary we could measure NT-proBNP level to support prognosis data and monitoring effectiv-

ity therapy especially ACE inhibitor which had antiremodelling effect towards patients with HF.

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