ANALYSIS OF CHANGE IN NT-proBNP AFTER ANGIOTENSIN RECEPTOR BLOCKER (ARB) THERAPY IN PATIENT WITH HEART FAILURE

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ABSTRAK

NT-proBNP merupakan suatu fragmen inaktif dari BNP yang disekresi oleh ventrikel jantung dalam kondisi meregang sebagai respon stress dinding ventrikel pada pasien gagal jantung. Sebagai marker spesifik fungsi jantung, peningkatan kadar NT-proBNP menunjukkan peningkatan derajat keparahan pada gagal jantung. Prinsip terapi gagal jantung yaitu modulasi sistem neurohormonal. Terapi ARB dapat memodulasi neurohormon pada sistem RAA, sehingga terjadi penurunan NT-proBNP. Penurunan kadar NT-proBNP melebihi variasi biologis (> 25%) menunjukkan adanya respon terapi. Penelitian prospektif observasional ini bertujuan untuk menganalisis perubahan NT-proBNP setelah terapi ARB pada pasien rawat jalan. Penelitian dilaksanakan pada September – Desember 2015. Pengambilan sampel darah dilakukan pada pasien yang memenuhi kriteria inklusi saat awal penelitian dan setelah 2 bulan terapi ARB. NT-proBNP diukur menggunakan IMMULITE® sebagai parameter primer dan serum kreatinin sebagai parameter sekunder. Terdapat 14 pasien yang memenuhi kriteria inklusi (11 laki-laki dan 3 perempuan) dengan terapi ARB yaitu Valsartan (64%), Telmisartan (22%) dan Candesartan (14%). Setelah 2 bulan terapi ARB, terjadi penurunan kadar NT-proBNP dari 3092,5 (216 – 32112) pg/ml menjadi 2135,5 (350 – 16172) pg/ml yang bermakna secara statistik (p=0,003). Sedangkan parameter sekunder serum kreatinin yang diubah menjadi eGFR juga mengalami perubahan dari 73,33 (37,05 – 266,68) ml/menit menjadi 81,04 (39,31 – 167,02) ml/menit tidak bermakna secara statistik (p=0,657). Jumlah pasien yang mengalami penurunan > 25% sejumlah 7 orang (50%). Pada penelitian ini, pemberian terapi ARB dapat merubah kadar NT-proBNP secara bermakna setelah 2 bulan terapi. ***(FMI 2016;52:305-309)***

Kata kunci: *NT-proBNP, Gagal Jantung Kronis, ARB*

ABSTRACT

NT-proBNP is an inactive fragment of BNP secreted by stretched ventricle as response to wall stress in patients with heart failure. As a specific cardiac marker, elevated NT-proBNP correlates well with heart failure severity. The principle of heart failure therapy is modulation on neurohormonal activation. ARB can modulate neurohormon on RAA system, that result in decreasing NT-proBNP level and favorable outcomes. Reduction in NT-proBNP more than biologic variability (> 25%) shows a therapy response.This study was to analyze change of NT-proBNP after ARB therapy in ambulatory HF patients. This observational prospective study was carried from September to December 2015. Blood sampling was performed on patients who meet the inclusion criteria of the study at first visit and after 2 months therapy. NT-proBNP was measured by IMMULITE® as primary parameter and creatinin as secondary parameter. There are 14 patients met the inclusion criteria of the study (11 males and 3 females). ARB therapy used in patients were Valsartan (64%), Telmisartan (22%) and Candesartan (14%). After 2 months ARB therapy, a decrease in level of NT-proBNP with initial median 3092.5 (216 – 32112) pg/ml to 2135.5 (350 – 16172) pg/ml respectively were statistically significant (p=0.003). And the secondary parameter creatinin serum convert to eGFR shows a change in eGFR with initial median 73.33 (37.05 – 266.68) ml/minute to 81.04 (39.31 – 167.02) ml/minute respectively were statistically not significant (p=0.657). There were 7 patients (50%) have a decrease > 25%. In this study, we found that ARB therapy can change NT-proBNP level significantly after 2 months therapy. ***(FMI 2016;52:305-309)***

Keywords: *Natriuretic Peptides; NT-proBNP; Heart Failure; Angiotensin Receptor Blocker*

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INTRODUCTION

Heart Failure is clinical syndrome that develops when the heart cannot maintain an adequate cardiac output to fullfil metabolism demand at rest and or activity. With low cardiac output lead to compensation mechanism that is neurohormonal activation to recover cardio-vascular function within normal homeostasis. Neuro-hormonal activation involved are RAA and sympathic nervous system activation that responsible for increasing water sodium retention, peripheral vaso--constriction, and cardiac contractility (Mann 2012).

Long term neurohormonal activation can eventualy worsen cardiac function (Colledge et al 2010).

BNP synthesized as proBNP consist of 108 amino acid by ventricle. When relased to blood circulation, proBNP cleaved by furin into BNP as active fragment consist of 32 amino acid and NT-proBNP as inactive fragment consist of 76 amino acid (Weber & Hamm 2006). NT-proBNP as a powerful biomarker had diagnostic and prognostic role in patients with heart failure. Elevated NT-proBNP correlates well with heart failure severity. Compare to other biomarker, NT-proBNP more specific because synthesized by cardiomyosit. NT-proBNP synthesized as response to wall stress, stretched ventricle and elevated intracardiac pressure (van Kimmenade & Januzzi 2012).

The principle of heart failure therapy is modulation on neurohormonal activation, which activated in heart failure pathophysiology. ARB can modulate neuro-hormon on RAA system, that result in decreasing NT-proBNP level and favorable outcomes. NT-proBNP have biologic variation around 11 – 20 % (Frankenstein et al 2009). Therefore decrease NT-proBNP more than biologic variation shows a therapy response (Troughton 2014, Januzzi 2012). The aim of this study was to analyze the change of NT-proBNP after ARB therapy in patients with heart failure and to evaluate the therapy efficacy based on decrease percentage of NT-proBNP.

MATERIALS AND METHODS

An observational prospective study was conducted at Cardiology Ambulatory Department Dr. Soetomo Teaching Hospital during September to December 2015. Patient selection based on inclusion and exclusion criteria. Inclusion criteria (1) patient diagnose with heart failure clas II-III aged 21-75 years old; (2) patient on ARB therapy maximal 3 month before enrollment; (3) patient or family agreed follow study. Patients with GFR <25 ml/menit and BMI >30 kg/m2 were excluded. Patients were elected by consecutive sampling, we took every patient who fulfills the criteria.

Blood samples were collected from all patients who meet inclusion criteria of the study at first visit (baseline) and after 2 month therapy. The blood collected for serum NT-proBNP measurement was centrifuged and kept at 80 -100C until the time of the measurement. NT-proBNP measurement was performed by the Siemens (DPC): IMMULITE® 1000 Immuno-assay analyzer. In this study, we used IMMULITE/ IMMULITE 1000 Turbo NT-proBNP kit.

Descriptive analyses were performed to determine demographic of thepatients, NT-proBNP profile and eGFR profile. To analyze the change of NT-proBNP and eGFR before and after 2 months therapy, we used paired t-test for normal distribution and Wilcoxon test for the other one.

RESULTS

During the study period, 16 consecutive patients with ARB therapy for heart failure were screened for eligibility. Of these, 14 patients were eligible. Baseline characteristic are shown in Table 1. In this study, heart failure mostly occur in male patients and within age > 50 years. The common etiology was coronary heart disease. Frequently used ARB was valsartan (64%) with cotherapy furosemide (93%) and spironolacton (64%).

Table 1. Baseline Characteristic

Characteristics (n=14)		n (%)
Sex	Female	3 (21)
	Male	11 (79)
Age	< 50	4 (29)
	50 – 75	10 (71)
Heart Failure Etiology	Coronary Heart Disease	5 (36)
	Cardiomyopathy	3 (22)
	Valvular Heart Disease	4 (28)
	HHD	2 (14)
Coexisting illnesses*	Atrial Fibrillation	2 (14)
	Diabetes Mellitus	3 (22)
	COPD	2 (14)
ARB	Valsartan	9 (64)
	Candesartan	2 (14)
	Telmisartan	3 (22)
Co-Therapy**	Furosemide	13 (93)
	Spironolactone	9 (64)
	Digoxin	7 (50)
	Acetosal	8 (57)
	Clopidogrel	3 (22)
	ISDN	3 (22)
	Warfarin	4 (28)
	Simvastatin	5 (36)

* One patient may have one or more coexisting illness
** One patient may have one or more co-therapy

Statistical analysis used for comparing baseline data and after 2 month data is Wilcoxon test for NT-proBNP levels and eGFR. eGFR was calculated from creatinin serum by Modification of Diet in Renal Disease (MDRD) formula. The results of this test are shown in Table 2. There are significant change of NT-proBNP between baseline and after 2 months therapy (p=0.003). While there was no significant change in eGFR baseline and after 2 months therapy (p=0,657).

In this study, change of NT-proBNP from baseline to 2 months after therapy shows a decrease pattern (shown in Fig. 1). In this study, 12 out of 14 had a decreased NT-proBNP from baseline, while the other 2 had an increased. But there were only 7 patients (50%) who had a decreased >25%. Among those 7 patients, 5 patients (71%) were given ARB with furosemide and spironolactone, while the other 2 (29%) with furosemide (shown in Fig. 2).

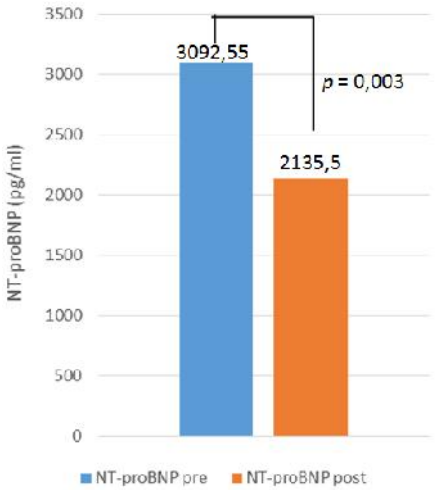

Fig. 1. Change of NT-proBNP profile

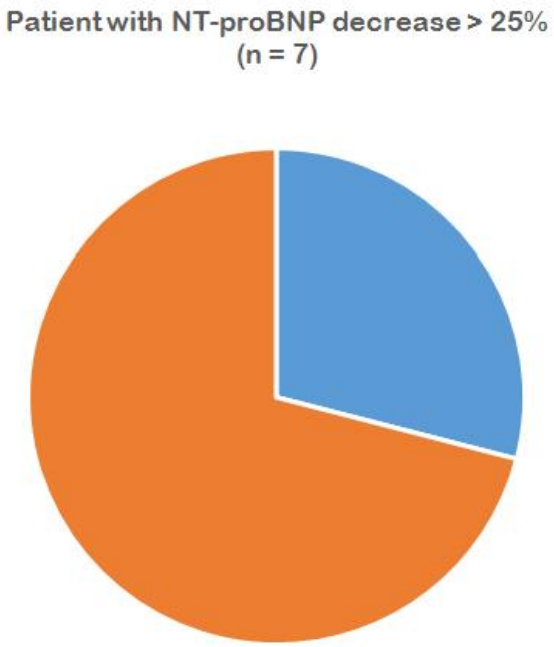

Fig. 2. Therapy evaluation profile

Table 2. Statistical analysis between baseline and after 2 months NT-proBNP & eGFR

Parameter	Baseline (pg/ml) [Median (Range)]	After 2 months (pg/ml) [Median (Range)]	Statistical Analysis	P value
NT-proBNP	3092.5 (216 – 32112)	2135.5 (350 – 16172)	Wilcoxon	0,003
eGFR	73.33 (37.05 – 266.68)	81.04 (39.31 – 167.02)	Wilcoxon	0,657

DISCUSSION

In this study, majority patients with heart failure were male patients (79%) and patients aged 50 – 75 years (71%). This conditions matched as previous epidemiological study, stating that heart failure incidency higher in male population and increased with age (Bui et al 2011). Based on epidemiological study state that common etiology of heart failure were coronary heart disease, and 36% patients in this study diagnosed with coronary heart disease (Old Miocard Infarction). During a period of days to months after an Acute MI, the infarcted area may expand as a result of dilatation and thinning of the left ventricular wall. These changes are known as ventricular remodeling. Because of these changes, the heart contract poorly and have distorted contraction and relaxation patterns. Finally, with low cardiac output may lead to activation of neurohormonal system as compensation mechanism, but chronic activation can eventually worsen the cardiac function (Page & Nappi 2013, Colledge et al 2010).

The principle of heart failure therapy is modulation on neurohormonal activation, which activated in heart failure pathophysiology. ARB can modulate neurohormon on RAA system, that result in decreasing NT-proBNP level on valsartan vs enalapril show decrease 15% vs 13% after 12 months therapy (Lee et al 2011, Masson et al 2008, Kasama et al 2006, Latini et al 2002). In this study, we also have similar result as previous study, that NT-proBNP decrease significantly (p=0,003) after 2 months therapy. NT-proBNP eliminated mainly by renal, so that renal insuficiency can reduce NT-proBNP clearence and NT-proBNP level increased. Some studies show that GFR correlates well with level NT-proBNP (Srisawadi et al 2010). In this

study show that no significantly change of eGFR after 2 months therapy and favorable outcomes. Previous study (Val-Heft) showed that valsartan can decrease BNP or NT-proBNP significantly ($p < 0,0001$) after 4 months. Some camparation study also show that ARB can decrease BNP or NT-proBNP significantly ($p < 0,05$) as effectively as ACEI. Study ($p=0,657$). Significantly change of NT-proBNP with no significant change of renal function (eGFR), demonstrated that renal function didn't contribute in changing NT-proBNP level.

NT-proBNP has biologic variation. Serial measurement of NT-proBNP (at day-14, month-1, month-2 and month-3) from pevious study show variability around 11 – 20 % (Frankenstein et al 2009). Therefore decrease NT-proBNP more than biologic variation shows a therapy response. In this study, we used RCV (Reference Change of Value) 25% to evaluate therapy (Januzzi 2012). Patients with NT-proBNP decrease > 25% shows effectivity therapy. There were 7 patients (50%) have a decrease > 25%.

Beside ARB, drug that involved in modulating neurohormonal system directly like antagonis aldosteron or beta blocker and indirectly like diuretic, may affect the level of NT-proBNP (Balion et al 2007). In this study, co-therapy that frequently used with ARB were furosemide (93%) and spironolacton (64%). In previous study (COLD-CHF), show that furosemide can change BNP, but not significantly ($p > 0,05$) compared with azosemide ($p < 0,05$) after 3 months therapy (Miyata et al 2012).

Another study, show that spirono-lakton can change BNP significantly ($p < 0,01$) after 4 – 6 months therapy compared to placebo (Feola et al 2003, Tsutamoto et al 2001). In this study, among 7 patients tha have a decrease > 25%, 5 patients (71%) were given ARB with furosemide and spironolactone, while the other 2 (29%) with furosemide (shown in Fig. 2). These shows that patients receiving ARB with furosemid and spironolactone had a better result than patients receiving ARB with furosemide. In this study, spironolacton contribute in decreasing NT-proBNP level together with ARB.

Our study has several limitations. First, this study has low sample size (because of health insurance system for limiting ambulatory patients on type-A hospital). Secondly, effectivity therapy less reflect because of short observation time. Third, we couldn't exclude patient with spironolactone because of limited sample and that's might affect the result of this study. A further study with a larger sample size and longer observation time is suggested.

CONCLUSION

In this study, we found that ARB therapy can change NT-proBNP level significantly after 2 months therapy.

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