Jurnal
Kardiologi Indonesia
J Kardiol Ind 2007; 28:19-26
ISSN 0126/3773

Clinical Research

Is Urinary Sodium a Surrogate Marker of Plasma Brain Natriuretic Peptide in ST Elevation Myocardial Infarction ?

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Background. High level of Brain Natriuretic Peptide (BNP) was suspected as a predictor of adverse events in acute ST Elevation Myocardial Infarction (STEMI). Unfortunately, the cost and availability of BNP assay had hampered its use. Natriuresis is one of the hallmark effect of raised BNP and measuring urinary sodium might offer insight to the plasma BNP. This study aims to search for any correlation between measured plasma BNP and urinary sodium in patients presenting with acute STEMI.
Methods. In an observational descriptive analytic study, we selectively included patients presenting with acute STEMI and checked for plasma BNP and urinary sodium. All patients had no symptoms or therapy of heart failure prior to admission, had no prior MI, had no valvular abnormalities, and had normal renal function. Plasma BNP was tested using immunoassay method from Abbot Diagnostics, while urinary sodium with ionic specific electrode method. Specimen for plasma BNP were taken at the admission while urinary sodium in the next morning, taking account of urine volume.
Results. There were 17 patients, 15 were (82.4%) men, with age 55.1$\pm$8.2 years old, onset of STEMI 18.6$\pm$2.3 hours, and left ventricular ejection fraction (LVEF) 47.6$\pm$11.6%. The urinary sodium was 85.1$\pm$34.3 mEq/L, and plasma BNP 449.7$\pm$48.8 pg/ml. Pearson's correlation and linear regression analysis showed positive correlation between urinary sodium and plasma BNP ($r = 0.71$). In multivariate analysis, plasma BNP ($p<0.01$) and LVEF ($p<0.05$) were the major influencing factors for urinary sodium level.
Conclusion. This study revealed a strong correlation between plasma BNP and urinary sodium in patients presenting with acute STEMI. While measurement of urinary sodium cannot replace plasma BNP, it might actually reflect plasma BNP level.

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(J Kardiol Ind 2007; 28:19-26)

***Keywords**: plasma BNP < urinary sodium < acute STEMI*

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Penelitian Klinis

Natrium Urin Petanda *Surrogate* Brain Natriuretic Peptide Plasma Pasien Infark Miokard dengan Elevasi ST ?

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Latar belakang: Kadar Brain Natriuretic Peptide (BNP) yang tinggi diduga merupakan prediktor kejadian buruk pada infark miokard akut dengan elevasi ST (ST Elevation Myocardial Infarction - STEMI). Akan tetapi pemeriksaan BNP mahal dan tidak mudah didapat, sehingga penggunaannya terbatas. Natriuresis merupakan salah satu efek menonjol dari kenaikan BNP, sehingga kemungkinan pengukuran kadar Natrium dalam urin dapat menggambarkan kadar BNP plasma. Penelitian ini bertujuan untuk melihat hubungan antara kadar BNP plasma dan kadar Natrium urin pasien STEMI akut.
Metoda. Penelitian ini merupakan studi analitik deskriptif observasional. Secara selektif disertakan pasien STEMI akut, kemudian diperiksa kadar BNP plasma dan Natrium urin. Semua pasien tak mempunyai keluhan atau mendapat terapi gagal jantung ketika masuk perawatan, juga belum pernah mengalami infark miokard sebelumnya, tak ada kelainan katup, dan fungsi ginjalnya normal. Kadar BNP plasma diukur menggunakan metoda *immunoassay* dari *Abbot Diagnostics*, sedangkan kadar Natrium dalam urin diukur dengan metoda *ionic specific electrode*. Sampel darah untuk mengukur BNP plasma diambil saat pasien masuk perawatan, sedangkan Natrium urin diukur keesokan harinya, mengingat diperlukan waktu untuk mendapat urin yang cukup jumlahnya.
Hasil. Ada 17 pasien yang memenuhi kriteria, 15 (82.4%) laki-laki, dengan usia 55.1±8.2 tahun, onset STEMI 18.6±2.3 jam, dan fraksi ejeksi ventrikel kiri (LVEF) 47.6±11.6%. Kadar Natrium urin 85.1±34.3 mEq/L, dan BNP plasma 449.7±48.8 pg/ml. Analisis hubungan *Pearson* dan regresi linier menunjukkan korelasi positif antara Natrium urin dan BNP plasma ($r = 0.71$). Pada analisis multivariat, terbukti bahwa BNP plasma ($p<0.01$) dan LVEF ($p<0.05$) merupakan faktor utama yang mempengaruhi kadar Natrium urin.
Kesimpulan. Penelitian ini telah membuktikan adanya hubungan kuat antara BNP plasma dengan Natrium urin pada pasien-pasien STEMI akut. Meskipun pengukuran Natrium urin tak dapat menggantikan BNP plasma, namun sebenarnya dapat merefleksikan kadar BNP plasma.

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Kata kunci : BNP plasma < Natrium urin < STEMI akut

The cardiac natriuretic peptide system is activated after AMI.[1,2] Morita et al.[3] were the first to demonstrate significantly elevated plasma Brain Natriuretic Peptide (BNP) levels on admission in 50 patients with ST-elevation acute myocardial infarction (STEMI) compared with controls, with peak levels were observed 16 h after onset. BNP is released by the ventricles as a neurohormonal response to increased wall stress and pressure and volume overload.[4,5] In a subsequent study, increase plasma BNP secretion may more accurately reflect regional wall stress in the infarcted region of the ventricle.[6] Increased regional wall stress is believed to be associated with adverse ventricular remodeling and a poor prognosis after STEMI.[7,8]

BNP has a spectrum of pharmacological activities such as diuretic, natriuretic, hypotensive, and smooth muscle relaxant activities and inhibition of the renin-aldosterone axis.[9,10] These effects are due to the stimulation of guanylate cyclase–linked natriuretic peptide receptors, leading to an increase in cGMP concentration in target cells.[10,11] The site of action of BNP is assumed at many level of nephron, including proximal and distal tubules as well as the inner medullary collecting duct. **Figure 1** shows the effect of BNP which increase intracellular cGMP level that leads to inhibition of sodium transport across cell.[11]

From a clinical perspective, evidence of close relation-ship between plasma BNP level and urinary sodium excretion is shown by a study done by La Villa et al.[12] They showed that acute incremental increase of plasma BNP level in normal individuals resulted in increase in urinary sodium excretion in a placebo-controlled, crossover study. Their study involved six healthy volunteers who received incremental infusions (0.25 pmol/kg per minute in the first hour and 0.50 pmol/kg per minute in the second) of synthetic human brain natriuretic peptide-32. BNP administration induced a significant 1.7-fold increase in urinary sodium excretion without affecting renal plasma, glomerular filtration rate and urine flow rate. Urinary sodium level showed an approximate 52% increase during the lower BNP dose (0.25 pmol/kg per minute) and a further 12% increment during the higher dose (0.50 pmol/kg per minute) as shown in **figure 2**. The cumulative increase in urinary sodium excretion induced by BNP infusion was therefore 70%.[12]

In addition to increase urinary sodium excretion, BNP also exerted an inhibitory effect on the renin-aldosterone axis, as indicated by the significant 50% or more decrease of plasma renin activity and urinary excretion rate of aldosterone. These results suggest that BNP may be involved in the overall regulation of body fluid and cardiovascular homeostasis in humans.[12] In conclusion of all the above literature reviews, it is theoritically plausible that the level of urinary sodium is correlated with the level of plasma BNP in a clinical setting.

There are problems perceived with BNP laboratory test. First is the cost of the BNP assay. Since all BNP assay available in Indonesian market is imported, the cost of laboratory examination is high. One laboratory test for BNP will cost Rp 200.000,- or more depending on the assay used. In Indonesia or in any low income countries, this amount of money is substantial. For many patients especially those who are

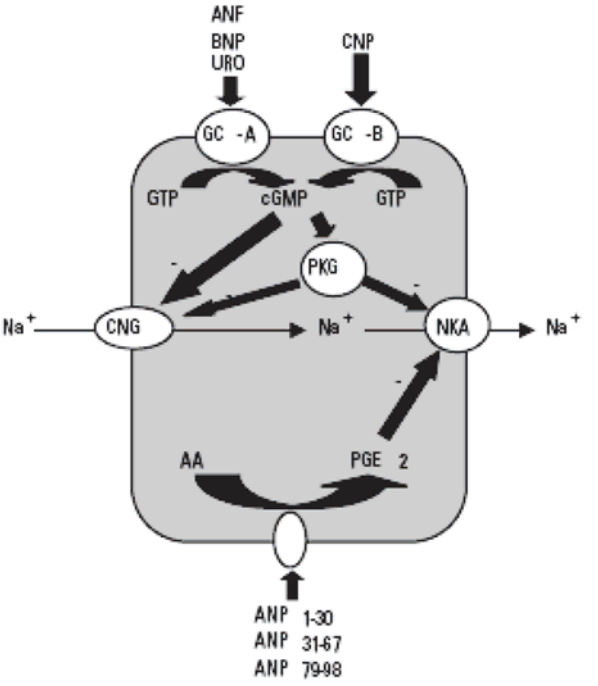

Figure 1. The mechanism of sodium transport inhibition by natriuretic peptides in inner medullary collecting duct.[11] GC-A – guanylate cyclase A, GC-B – guanylate cyclase B, PKG – protein kinase G, CNG - cyclic nucleotide-gated cation channel, NKA– Na+, K+-ATPase, AA – arachidonic acid, PGE2 – prostaglandin E2, ANF – atrial natriuretic factor, BNP – Btype natriuretic peptide, URO – urodilatin, CNP – C-type natriuretic peptide.

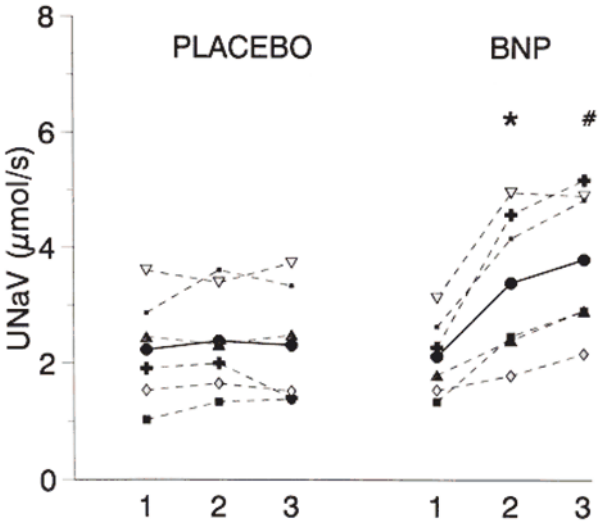

Figure 2. Increase urinary sodium excretion after administration of BNP.[12] Line graphs show mean (solid line) and individual (dashed lines) values of $U_{Na}V$ in the three clearance periods performed during administration of placebo and BNP (1=baseline, 2=0.25 pmol/kg per minute, 3=0.50 pmol/kg per minute).

not covered with insurance or patients who their insurance will not reimburse BNP test, the amount of money incurred for BNP test may be better allocated to purchase medications. Second problem is the availability of BNP assay. At least for now, laboratory test to measure plasma BNP level can only be performed in large medical laboratory or in provincial hospital. While importance of BNP assay has already recognized, district (kabupaten) hospital should be given opportunity to take full advantage of this new test. Furthermore, the problem of availability of BNP assay may have underlying laboratory resources deficiency within the district hospital, either the assay itself, equipment or manpower. Considering these two present problems with plasma BNP assay, the reasearchers were looking for any alternative but less costly laboratory test that has significant correlation with plasma BNP. One candidate laboratory test is urinary sodium, not only because it physiologically increased when plasma BNP is elevated as shown by previous literature, but also urinary sodium test costs only one-tenth of plasma BNP test. But in order to use urinary sodium as an alternative to plasma BNP, their correlation in clinical patients should be determined. On academic ground, it was surprising enough that there were no published literature (using Medline, Highwire and other document searches) demonstra-ting the correlation between plasma BNP and urinary sodium in the setting of clinical STEMI patients. These two arguments: problems of BNP assay and no previous study relating urinary sodium and palsma BNP in a clinical setting signify our rationale for conducting this study. Therefore the objective of this study is to search for any correlation between plasma BNP and urinary sodium in patients presenting with STEMI. Further validation of their correlation would be supported by looking for factors that influence urinary sodium level in patients presenting with STEMI.

Methods

The design of this study was observational descriptive analytic, recruiting patients presenting with STEMI. The study was conducted during 3 months period (between November 2005 through January 2006) at National Cardiovascular Center "Harapan Kita" Jakarta. Patients were selected at admission, either in the emergency department or in the intensive cardiovascular unit.

Selection of patients was based on the predetermined inclusion criteria, which are: no symptoms/signs and or therapy of heart failure prior to admission, no prior MI, no valvular abnormalities, and normal renal function. Symptoms of heart failure include exercise intolerance, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, peripheral edema. Signs of heart failure was verified by the presence of cardiomegali, S3, basal pulmonary rales, elevated jugular pulse, hepatomegaly and leg edema. Therapy of heart failure may consist of ACE inhibitors, diuretics, beta blockers, digoxin. But for the majority of patients, medical record was the main source for the determination of heart failure prior to admission. Prior MI proved to increase BNP level[13] and it was determined by searching previous history from medical record or by looking at evidence of pathologic Q wave on the 12-lead electrocardiography. Transthoracal echo-cardiography was performed in all patients on the day 3 - 4 of hospitalization where left ventricular ejection fraction was recorded. Any significant (more than trivial) valvular abnormalities was noted and patients with significant valvular regurgitation was excluded.

Determination of patients selected to be recruited in the study was done by 2 researchers working independently, and all patients who fulfill the inclusion criteria was recruited consecutively. Patients selected were then recorded with regards to their age, sex, onset of STEMI, risk factors (especially hypertension and diabetes mellitus), infarct location, and other important characteristics including previous drugs that has been consumed.

Plasma BNP level was determined at admission or at the earliest time after being selected, using immunoassay method from Abbot Diagnostics. Overnight urine was collected using standard collection method at the intensive cardiovascular unit and checked for urinary sodium in the next morning. Overnight urine was used as the collection protocol due to previous study by Kamata et al[14] and Tsai et al[15] that showed overnight urine was easy and reliable for the estimation of sodium excretion for 24 hours. Overnight urine was also chosen because of practicality and simplicity of specimen collection compared with the standard 24 hours urine collection. Urine volume of each patients were also recorded. Urinary sodium level was determined using ionic specific electrode method. Aside of plasma BNP and urinary sodium, all patients was also examined for plasma sodium, plasma creatinine, plasma ureum, plasma glucose as a routine laboratory examination.

Overnight therapy for STEMI patients was verified for any diuretics or high dose ACE inhibitors, since these two drugs may interfere sodium excretion in the urine. High dose ACE inhibitors was loosely defined as Captopril 3x25 mg or more, or its equivalent dosage with other ACE inhibitors. Patients who received these drugs were also excluded.

Descriptive statistics (proportion, mean, standard deviation), Pearson correlation and multiple regression analysis were used for analysis, using software SPSS for Windows v.10 and Statistica foe Windows v.6.

Result

There were a total of 78 STEMI patients during 3 months period, starting from November 2005 to January 2006. Using the above inclusion criteria, we selectively recruited 24 patients (54 were excluded). Seven out of these 24 patients were further excluded due to their overnight therapy which consisted of diuretics or high dose ACE inhibitors, leaving the remaining 17 patients as study subjects. Only one patient had trivial mitral regurgitation on transthoracal echocardiography hence all of these 17 patients represent the final sample population for this study.

Table 1 shows several important characteristics of study subjects. Some interesting points in this table are the onset of STEMI which had a wide variation that may cause difference in the plasma BNP concentration. Although mean onset of STEMI in our study was 18 hours which was an ideal time to measure plasma BNP concentration (peak level achieved at 16 hours of onset), earlier onset relates to lower plasma BNP level.

Table 1. Patients characteristics

Characteristics	n (N=17)	Percentage or Mean ± SD
Age (years)		55 ± 8.2
Onset STEMI (hours)		18 ± 13.4
Sex: - Male	14	82.4
- Female	3	17.6
Hypertension	10	58.8
Diabetes mellitus	6	35.3
Infarct: - Anterior	7	41.3
- Inferior	8	47
- Both	2	11.7
Revascularization:		
- Thrombolytic	5	29.4
- PCI	4	23.5
LV Ejection Fraction (%)		47 ± 11.6

Hypertension and diabetes mellitus are well-known risk factors that have impact on left ventricular diastolic function. Reduced diastolic function also increase plasma BNP level shown by previous studies.[16, 17] This study incorporated high proportion of hypertensive patients which may have elevated baseline plasma BNP level.

Slightly more than 50% of our patients underwent coronary revascularisation, either by thrombolytic or percutaneus coronary intervention. Group analysis comparing urinary sodium and plasma BNP in patients with or without coronary revascularisation would be interesting but we did not perform group analysis because of small sample population.

Table 2. Laboratory values

Laboratory	Mean ± SD
Plasma sodium (mEq/L)	139 ± 3.7
Plasma creatinin (mg/dL)	1.0 ± 0.3
Plasma glucose (mg/dL)	186.5 ± 54
Plasma BNP (pg/mL)	449 ± 48.8
Urinary sodium (mEq/L)	85 ± 34.3

Plasma BNP levels were substantially higher in patients with STEMI than normal value (less than 100 pg/mL). This finding conforms with previous observation by Morita et al.[3] As predicted, this high plasma BNP concentrations correspond to the increase in urinary sodium level (normal value less than 40 mEq/L for overnight urine). Other laboratory values are not remarkable. Some patients, in particular diabetics, had increase plasma glucose level. As has been known, high plasma glucose level will affect urinary volume and thus urinary sodium concentration.

This study produced a significant correlation coefficient between plasma BNP and urinary sodium. The regression line with 95% confidence interval was shown (**Figure 3**). Although the coefficient is high, it would probably be difficult to apply this result in the population of STEMI patients as the sample population is too small. Larger sample may decrease this coefficient correlation, in accordance of the statistical theorem of regression toward the null.

Although the researchers exercise effort on minimizing confounding factors by applying quite strict inclusion criteria, several variables may still potentially affect the plasma BNP level and therefore urinary sodium level. Multiple regression analysis was chosen to check which variables acts as confounding factors for urinary sodium level. This method was performed by selecting urinary sodium as the dependent variables and the following factors as the independent variables: age, hypertension, diabetes, infarct location, onset, plasma glucose, plasma BNP, LVEF, plasma creatinine, and plasma sodium. This analysis was also carried out to reveal the most important variables that affect urinary sodium. Table 3 shows two statistically significant variables that influence urinary sodium level.

The result of multivariate analysis further confirm the existence of relationship between plasma BNP and urinary sodium. As only two variables: plasma BNP and left ventricular ejection fraction determine urinary sodium level, other possible factors that may influence urinary sodium level is statistically excluded. It has been recognized that plasma BNP increase when

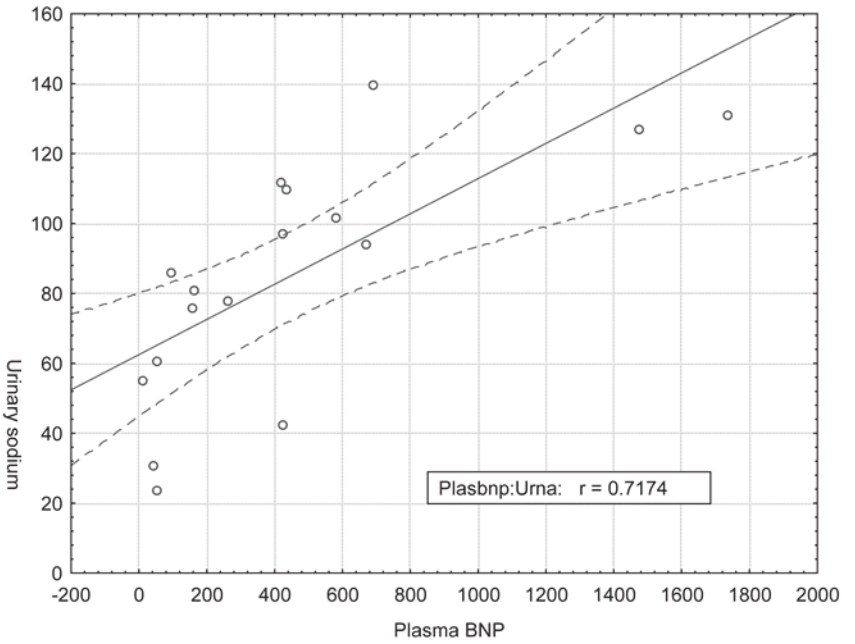

Figure 3. Correlation between plasma BNP and urinary sodium

left ventricular ejection fraction is significantly reduced, reflecting left ventricular volume or pressure overload. We speculate that in our patients, low ejection fraction works by raising plasma BNP level and the latter will eventually increase urinary sodium concentration.

Discussion

This study utilized an observational, descriptive analytic design. In this kind of study, careful attention must be paid to limit the confounding factors which may interfere with the results of the study. Therefore the researchers set rigid inclusion criteria which hopefully can ward off any possible confounding factors. As a result of these inclusion criteria, the number of patients who could be recruited was low and might have influenced the power of this study. This approach was selected in the view of better validity at the expense of low study power. Low powered study increased type B error and the end result might be overestimation of the true population value, in this case the coefficient correlation. Larger patients recruitment is the only solution to the low powered study.

Several factors such as sodium and water intake, hydration status, inaccuracy of urine collection, and ingestion of certain drugs might cause error in the determination of urinary sodium level. Moreover, there might be differences in the above factors among patients and homogenous population of patients could not be achieved. The researchers realized that it might be extremely difficult to reach homogeneity of patients for this study since sodium and water intake prior to admission is virtually impossible to control. But even in a well designed, randomized study, water and sodium intake prior to admission of STEMI patients is difficult to control. Controlled study has the advantages of comparison with different population which can confirm the findings of the study. Control population of normal individuals might have different plasma BNP level compared to STEMI patients. If there exists a correlation between plasma BNP and urinary sodium in the control population, it can further confirm the existence of association between plasma BNP and urinary sodium. This study was lacking of control population due mainly to financial resources.

The results of this study has to be interpreted carefully that it could only be applied to a specific subset of STEMI patients. These specific patients are those without preexisting heart failure or those without therapy for heart failure. In patients with preexisting heart failure, plasma BNP level has already high and thus urinary sodium excretion will increased. Therapy of heart failure consists of ACE inhibitors, with or without diuretics. These two class of drugs cause higher sodium excretion in the urine. The same reasons also true for patients with previous myocardial infarction which may have increased plasma BNP level on the background. Renal failure intervene sodium handling of the kidney and causes increase or decrease sodium reabsorbtion in the proximal and distal tubules, and therefore the results of this study could not be applied in patients with renal insufficiency

The clinical implications of the demonstration of statistically significant associations between these two laboratory tests depend not only on the strength of the association but also on practical aspects of the assay, such as the stability of the substance to be measured and the applicability and versatility of the biochemical analysis in question. We believe that sodium in the urine is relatively stable under normal condition hence its concentration is reliable to measure. On the practical point of view, the only hassle to measure urinary sodium is the collection of urine.

On the positive side, this study represent the first to address association between plasma BNP and urinary sodium in clinical STEMI patients. It would be imperative that this research can encourage further research in this field with more sample and control in order to verify our findings.

Conclusion

We found a strong correlation between plasma BNP and urinary sodium in a specific subset of patients presenting with STEMI. Measurement of urinary sodium might actually reflect plasma BNP level, but whether urinary sodium can be a surrogate marker for plasma BNP need to be further validated.

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