An Equation to Explain Variations in Blood NT-ProBNP in Ambulatory Cardiac Subjects

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Background: *NT-proBNP is being used as a biomarker for prognosticating and delineating cardiac dysfunction. The cut-off value for deciding normal versus abnormal levels has always been a point of contention since it depends on the degree of dysfunction as well as other associated conditions often termed non-cardiac factors and parameters. Such association had not been formally presented.*
Objective: *To determine the direction and magnitude of effect of cardiac and non-cardiac parameters on NT-proBNP variability.*
Material and Method: *The present study included 78 cardiac ambulatory patients with a history of heart failure and/or low left ventricular ejection fraction. Their cardiac and non-cardiac parameters were recorded at the time of blood sampling for NT-proBNP. Multivariate linear regression analysis was used to correlate cardiac and non-cardiac parameters with NT-proBNP level and, from this, a predictive equation was derived.*
Results: *Log [NT-proBNP (pmol/l)] was 1.424 + 0.348 (for EF of 18-27) + 0.636 (for EF < 18) + 0.021 CTR - 0.002 SMW - 0.326 for female + 0.430 Cr - 0.010 BW. [EF = LV ejection fraction in %; CTR = cardio-thoracic ratio in %; SMW = 6-minute walking distance in meters; Cr = serum creatinine in mg/dl; BW = body weight in kg]. The adjusted R-square for this regression was 0.659. Omitting the non-cardiac variables (sex, Cr, BW) would decrease the adjusted R-square to 0.493.*
Conclusion: *Cut-off value for NT-proBNP concentration in subjects without severe systolic heart failure has to account for these non-cardiac factors.*

Keywords: *NT-proBNP, Natriuretic peptide, Heart failure, Variability*

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Blood B-type natriuretic peptide (BNP or NT-proBNP) is one of the foremost biomarkers for diagnosing, prognosticating and monitoring heart failure and right and left ventricular dysfunction[1-3]. Studies in patients with these conditions or in patients with different settings show that not only cardiac factors but some non-cardiac factors such as age, sex, physical structure, and renal function also affect the peptide level[4,5]. In the presence of very high levels of this marker, e.g. in severe acute heart failure, these non-cardiac factors probably have minimal contributory roles since the diagnosis is not in doubt and the level of the peptide would be very high. The same principle probably applies if this marker is used to follow the change in status in individual subjects. In contrast, if this marker is to be used in a large community-based cohort[6,7], or in an outpatient setting to decide whether to send the patient for a more sophisticated examination such as echocardiogram for suspected cardiac dysfunction[8], or in ambulatory heart-failure clinic[9,10],

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these non-cardiac factors will affect the threshold or cut-off value. Few studies had looked at specific contribution of these non-cardiac factors in association with the cardiac abnormalities. Among the 72 reports that Balion et al. reviewed, only seven looked at the relationship in a multivariate sense[5]. The present report arose from following up a group of patients with symptomatic heart failure or asymptomatic left ventricular dysfunction with assessment of their blood NT-proBNP as well as other cardiac and non-cardiac variables such as echocardiographic variables, electrocardiographic intervals, age, sex, serum creatinine, and body weight. This allowed the relationship of these other factors towards NT-proBNP variability to be determined.

Material and Method

Ambulatory cardiac patients with either a history of heart failure or poor left ventricular systolic function from two medical schools were selected for their willingness to be clinically reviewed, to have their blood taken and do a 6-minute walk. All signed the informed consent allowing the extra procedure related to the review of their cardiac status. The informed consent and study protocol had passed the scrutiny of the ethics committees of both medical schools. None of the patients was in an unstable stage or needed drug adjustment. Fifty of 78 patients had a history of heart failure, while the remaining 28 who had no heart failure had been followed up for their impaired left ventricular systolic function.

Transthoracic echocardiograms were performed by cardiologists who regularly did this procedure (> 50/month) for the last 10 years (WJ, SS, AP). The following variables were also recorded: history related to heart failure, present and initial functional classes according to the New York Heart Association (NYHA-FC), anthropometry, and general physical examination especially of the cardiovascular system. Blood was taken for creatinine (Cr) and NT-proBNP. This was followed by a 6-minute walk, which in eight instances could not be accomplished because of fatigue, claudication, or arthritis. The electrocardiogram (ECG) and chest roentgenogram (CXR) were repeated if these were not done within the previous year.

Serum from freshly collected blood was immediately separated and stored at -20 degree C. Specimens were processed in batches using the electrochemiluminescence technique (Elecsys 2010 and E170, Roche Diagnostics, Thailand, who also supplied the reagent). Outliers were repeated. Coefficient of variation for repeated measurement in our laboratory was less than 3% for concentrations of 40-700 pmol/l (conversion: pg/ml = 8.475 pmol/l).

Cardiothoracic ratio (CTR) was conventionally measured from the CXR. Intervals and other measurements in the ECG were recorded from the automatic print-out. Distance achieved in the six-minute walk (SMW) was expressed in meters. Measurements obtained from the echocardiogram were further categorized. Left ventricular ejection fraction (EF), by visual estimation, was separated into five groups as EF < 18, 18-27, 28-37, 38-47, and > 47% to circumvent digit preference[11]. The authors determined diastolic function from those with sinus rhythm, using ratio of mitral E to A wave velocities (n = 57) from pulse doppler, and velocity of propagation (Vp) of early filling from mitral annulus to left ventricular apex using color M-mode doppler[12,13]. Valvular leaks, independent of their valve-sites and nature i.e. either organic valvular diseases or secondary to cardiomyopathy, were graded from the color flow map into three groups: none, mild, and more than mild, this last included patients with mild abnormalities but involving > 1 valve.

Statistical analysis

NT-proBNP values were logarithmically ($\log_{10}$) transformed (log [NT-proBNP]). Continuous variables were expressed as mean and standard deviation (SD). Multivariate linear regression for factors related to log [NT-proBNP] was done starting with echocardiographic parameters (i.e. EF, diastolic function, and valvular abnormality). This was followed by adding variables derived from ECG (i.e. atrial fibrillation or sinus rhythm, QRS duration, corrected QT interval) and CXR (CTR), then the vital signs (systolic and diastolic blood pressures, heart rate) and the SMW followed by NYHA-FC obtained initially and NHHA-FC when blood for NT-proBNP was taken. At each step except the last, variables were removed if the partial F-test yielded a p-value of > 0.1. In the final step, the p-value for removal was reduced to > 0.05. The final step included sex, age, Cr, and body weight (BW). Adjustments were made for missing values in the independent variables. Separate categories were created for missing values of categorical variables and included together with non-missing categories in the regression models. For continuous variables, missing values were replaced by the mean of all non-missing values and a new dummy variable created to indicate missing status. The dummy variable was always included in models containing the variable with

replaced values. Statistical significance of variables with missing data was in all cases determined only for the non-missing data. Model assumptions of normality and homoscedasticity of residuals were examined by observing residual plots.

Results

Seventy-eight patients (64 from Songklanagarind Hospital and 14 from Chiang Mai University Hospital) were enrolled. Fifty-six had low ejection fraction, which the authors considered as cardiomyopathy (< 40%). Ischemic cardiomyopathy was diagnosed in 40 patients with either a history of myocardial infarction or coronary angiogram showing significant coronary stenosis. Other patients included three subjects with prosthetic heart valve associated with EF of 10-20%, and 12 with aortic or mitral regurgitation. There were 22 with diabetes mellitus. Seven had a previous history of stroke.

Their mean age (SD) was 60.3 (13.1), range from 15 to 78 years. Sixty, out of 78 (77%), were males. The distributions of subjects by NYHA-FC I-IV were 38, 21, 16, and 3, respectively. Eleven cases were in chronic atrial fibrillation. Chronic medications included spironolactone (44%), betablocker (63%), angiotensin converting enzyme inhibitor (76%), digoxin (22%), and diuretics (76%). Selected characteristics of the group are shown in Table 1. Of the 57 subjects in whom diastolic functions could be determined, 16 were normal, 25 were classed as relaxation abnormality, four were pseudonor malization, and 12 showed restrictive filling patterns.

Log [NT-proBNP (pmol/l)] ranged from 0.24 to 3.55. Fig. 1 demonstrates that log [NT-proBNP] level was inversely related to EF only up to an EF of around 40%. In univariate analysis, log [NT-proBNP] was related (Spearman's rho, p-value) to: NYHA-FC (0.564, < 0.001), heart rate (0.258, 0.022), SMW (-0.534, < 0.001), left ventricular systolic dimension (0.480, < 0.001), left ventricular diastolic dimension (0.355, 0.002), EF (-0.574, < 0.001), severity of valvular leak (0.421, < 0.001), QRS duration (0.416, < 0.001), corrected QT interval (0.478, < 0.001), CTR (0.594, < 0.001), Cr (0.333, 0.003), and BW (-0.412, < 0.001), but was not for female sex (0.047, 0.681) or age (0.123, 0.284).

The first step of multivariate regression showed that the differences in EF, diastolic function, and severity of valvular regurgitation explained less than half of log [NT-proBNP] variability (adjusted R square = 0.358, data not shown). The final models of multivariate regression analysis before and after collapsing the levels of ejection fraction are shown in Table 2, and as seen, age was not accepted as being contributory. The final equation for log [NT-proBNP (pmol/l)] is 1.424 + 0.348 for EF from18% to 27% + 0.636 for EF below 18% + 0.021 CTR (%) - 0.002 SMW (meter) - 0.326 for female + 0.430 Cr (mg/dl) - 0.010 BW (kg). Adjusted R square of this model was 0.659 but would only be 0.493 if the non-cardiac variables (sex, serum creatinine, and body weight) were omitted.

Fig. 2 shows a scatter plot with the line of identity and best fitted regression line for predicted and measured log [NT-proBNP]. The correlation (r) of the predicted values with the measured was 0.836.

Table 1. Selected characteristics in 78 subjects

Log [NT-proBNP (pmol/l)]	2.05 ± 0.68
Systolic/diastolic blood pressures, mmHg	123.0 ± 25.0/69.0 ± 12.0
Heart rate, minute	74.1 ± 16.8
Body weight, kg[a]	62.4 ± 12.9
Serum creatinine, mg/dl[a]	1.51 ± 0.48
Cardio-thoracic ratio, %[b]	59.1 ± 9.2
QRS duration/corrected QT interval, msec	102.5 ± 26.1/435.5 ± 43.4
6-minute walk, meter[c]	392.9 ± 127.4
LV ejection fraction, %	35.3 ± 16.4
EF < 18%, 18-27%, 28-37%, 38-47%, > 47%	8, 22, 16, 14, 18 subjects
LV dimensions (diastolic/systolic), mm	61.9 ± 11.7/48.5 ± 13.4
MV e-wave velocity, cm/sec[d]	74.7 ± 25.7
E/A[e]	1.36 ± 0.82
Velocity of propagation, cm/sec[f]	42.8 ± 13.9

The values are mean ± SD, unless otherwise specified
LV = left ventricle, MV = mitral valve, E/A = ratio of mitral valve E to A wave-velocities
Number of subjects for a, b, c, d, e, f = 77, 73, 70, 58, 57, 63 respectively

Table 2. Final and reduced linear regression models using log [NT-proBNP (pmol/l)] as the dependent variable and other parameters as independent variables

Model	Variable	Coefficient	95% confidence limits	p-value	Adjusted R^2
Final step (unreduced)					0.654
	EF>47%	0			
	EF 38-47%	-0.058	-0.359, 0.244	0.704	
	EF 28-37%	0.106	-0.189, 0.401	0.476	
	EF 18-27%	0.377	0.065, 0.690	0.019	
	EF<18%	0.678	0.261, 1.094	0.002	
	CTR (%)	0.019	0.005, 0.034	0.009	
	SMW (meter)	-0.002	-0.003, -0.001	0.001	
	Sex:female	-0.332	-0.613, -0.052	0.021	
	Creatinine (mg/dl)	0.408	0.190, 0.626	0.000	
	Weight (kg)	-0.011	-0.020, -0.002	0.017	
Reduced form					0.659
	EF >27%	0			
	EF 18-27%	0.348	0.086, 0.611	0.010	
	EF<18%	0.636	0.260, 1.011	0.001	
	CTR (%)	0.021	0.007, 0.035	0.004	
	SMW (meter)	-0.002	-0.003, -0.001	0.000	
	Sex:female	-0.326	-0.596, -0.055	0.019	
	Creatinine (mg/dl)	0.430	0.218, 0.643	0.000	
	Weight (kg)	-0.010	-0.019, -0.001	0.016	

EF = left ventricular ejection fraction, CTR = cardiothoracic ratio, SMW = distance attained with the 6-minute walk.

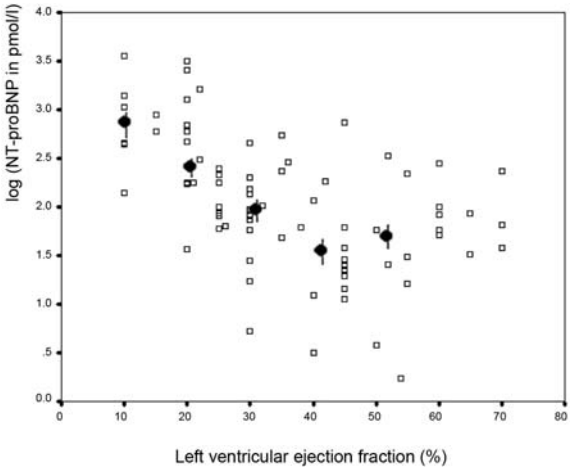

Fig. 1 The relationship between log [NT-proBNP] and left ventricular ejection fraction shown as a scatter plot (□) and in terms of groups (• for mean, and "|" for standard error). Means of log [NT-proBNP] were 2.86, 2.41, 1.97, 1.55, and 1.70 for EF groups of < 18, 18-27, 28-37, 38-47, and > 47% respectively

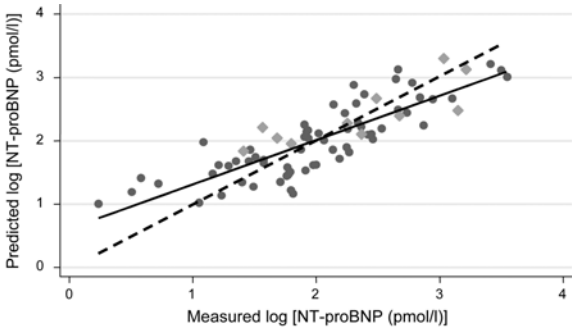

Fig. 2 Relationship between predicted log [NT-proBNP] and measured log [NT-proBNP]. Predicted values were calculated from the final (reduced) regression model. Pearson correlation coefficient for 65 patients with no missing predictors is 0.836. The regression equation for predicted on measured log [NT-proBNP] is: Predicted log [NT-proBNP] = 0.611 + 0.700 measured log [NT-proBNP]. • Patients with no missing predictors, ♦ Patients with missing predictors, - - - Line of identity, — Regression of predicted on measured log [NT-proBNP]

Discussion

The present analysis showed that in this specific out-patient population (with heart failure and/or with systolic and diastolic dysfunctions), the multivariate regression model accounts for two thirds (adjusted R square was 0.659) of the variation in log [NT-proBNP]. The adjusted R-square dropped to 0.493 if only echocardiographic variables and indirect cardiovascular features and performance (EF, cardiac silhouette, 6-minute walk) were selected. Among these, cardiothoracic ratio or 6-minute walk each contributed about 5%. Non-cardiac factors (body weight, serum creatinine, and sex) accounted for 16% of the total fit, and serum creatinine contributed to half of the non-cardiac factors.

Previous reports had already shown the relation of cardiac and non-cardiac variables to blood NT-proBNP levels[1-5,14,15]. However, most studies either used univariate analysis or, when multivariate analysis was done, were concerned mainly with looking at specific relationship of one parameter with the peptide level, utilizing few other variables only to adjust for the differences between groups. Some studies concentrated only on obesity vs. the peptide[16,17]; some, the peptide variability as a function of age and gender[18-22]; few examined the several variables together. These came about presumably because the study was directed towards the population examined, such as, the very sick[23], patients with symptomatic heart failure[1,3,17,22], a general population or patients from general practices[2,16,18-21]. Among the reports that provided coefficients for the non-cardiac variables, the independent positive predictors for the higher peptide value were age and Cr, while the negative factors were BMI or obesity indices and diabetes or HbA1c[2,18]. For the cardiac variables, EF had to be a negative risk, but as shown in Fig. 1 and as Loke et al[19] had pointed out, there is an EF threshold where NT-proBNP loses its predictive value.

The present analysis did not accept age, either univariate- or multivariate-wise, as being related to the blood level of the peptide in these outpatient subjects. Despite the wide age-range of 15-78 years, the distribution was left-skewed with three-fourths of patients being older than 50 years. With regard to female sex, the present regression model showed that female sex was negatively associated with the blood level of this marker. Balion et al stated that out of 11 reports where the relationship with peptide level was examined, only five showed positive relationship[5]. These five had larger numbers of subjects. Twenty three percent of the present patients were female. The literature review showed that the effect of female sex on NT-proBNP can be either nil or positive[1-2,14,18-22] but not negative. If the evaluation was done in a general population, being female correlated with higher peptide concentration[18-21]. However, if the evaluated population consisted of those with symptomatic heart failure (acute[1] or chronic[14,22]), female sex had no effect. In a separate interrogation of the model (data not shown), if body mass index replaced body weight, the effect of sex on log [NT-proBNP] became statistically non-significant, while the predictability of the other variables remained. The alteration with regard to selected variables is seen if creatinine clearance (Cockcroft-Gault formula) replaced serum creatinine in another separate model-interrogation, the adjusted R square decreased to 0.619, while body weight was no longer significant in the equation for determining log [NT-proBNP].

The major limitations of the present study include the incomplete collection of some variables where substitutes may not be adequate, the small number of observations, and possibly the lack of inclusion of other potentially related variables, e.g. hemoglobin, which has been reported to affect this peptide[24,25]. It is interesting that anemia, renal failure, and insulin insensitivity are now accepted as being closely related to heart failure. These limitations may explain in part the somewhat low value of adjusted R square in the multivariate regression model for log [NT-proBNP] in this study.

Conclusion

If a cut-off value of NT-proBNP is being used as a marker towards decision making on the management of patients as a group, one must consider other allied cardiac factors such as CTR, physical performance, and non-cardiac factors such as physical characteristic and renal function. A single "threshold" NT-proBNP level should never be used without these considerations.

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Disclosure

We received no fee or consulting honoraria

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สมการที่อธิบายความแปรปรวนของระดับเอ็นที-โปรบีเอ็นพีในเลือดในกลุ่มผู้ป่วยโรคหัวใจที่คลินิกผู้ป่วยนอก

ศรัณยู สุวรรณอักษร, ธาดา ยิบอินซอย, อลัน กีเตอร์, วรวุฒิ จินตภากร, อรินทยา พรหมินธิกุล

***ภูมิหลัง**: ระดับเอ็นที-โปรบีเอ็นพี (NT-proBNP)ในเลือดมีการใช้อย่างแพร่หลายเพื่อช่วยประเมินความรุนแรง และทำนายความเสี่ยงที่เกิดจากความผิดปกติของหัวใจ ในกรณีที่ระดับ เอ็นที-โปรบีเอ็นพี ไม่สูงมากเช่นที่มาจากการติดตามผู้ป่วยที่ไม่มีภาวะหัวใจวายอย่างรุนแรง จะพบว่าระดับเอ็นที-โปรบีเอ็นพีขึ้นกับปัจจัยในร่างกายที่ไม่สัมพันธ์กับการทำงานของระบบหัวใจด้วย เป็นจุดประสงค์ของรายงานคือวิเคราะห์ผลกระทบจากปัจจัย 'นอกหัวใจ' นี้*

***วัสดุและวิธีการ**: วิเคราะห์ความสัมพันธ์ระหว่างระดับเอ็นที-โปรบีเอ็นพีในเลือดและตัวแปรที่วัดด้านการทำงานของหัวใจและตัวแปรนอกหัวใจในผู้ป่วยโรคหัวใจที่คลินิกผู้ป่วยนอกจำนวน 78 ราย ใช้สถิติสมการถดถอยเชิงพหุเพื่อแปลงเป็นสมการทำนายระดับเอ็นที-โปรบีเอ็นพีในเลือด*

***ผลการศึกษา**: สมการที่ได้คือ log ฐานสิบของเอ็นที-โปรบีเอ็นพี = 1.424 + 0.348 LVEF (ค่าการบีบตัวหัวใจห้องล่างซ้าย) ถ้าอยู่ในช่วง 18% ถึง 27% + 0.636 ถ้า LVEF น้อยกว่า 18 % + 0.021 CTR (สัดส่วนของหัวใจต่อช่องอก, %) - 0.002 x ระยะทางที่เดินได้ใน 6 นาที (เมตร) - 0.326 กรณีผู้ป่วยเพศหญิง + 0.430 x ระดับครีเอตินินในเลือด (มิลลิกรัมต่อเดซิลิตร) - 0.010 x น้ำหนักตัว (กิโลกรัม) สมการนี้อธิบายความแปรปรวนของค่า log ฐานสิบของเอ็นที -โปรบีเอ็นพี ได้ร้อยละ 65.9 กรณีที่ไม่คำนึงถึงตัวแปรเพศ, ระดับครีเอตินิน, และน้ำหนักตัว จะสามารถอธิบายความแปรปรวนได้เพียงร้อยละ 49.3*

***สรุป**: ระดับเอ็นที-โปรบีเอ็นพี ที่สูงผิดปกติในกลุ่มผู้ป่วยโรคหัวใจที่คลินิกผู้ป่วยนอกมี ผลกระทบจากปัจจัยนอกหัวใจ*