Serum N-Terminal Pro-Brain Natriuretic Peptide in Normal Thai Subjects

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Abstract

Aminoterminal portion of pro-brain natriuretic peptide (NT-proBNP) appears to be useful in the screening, diagnosis and prognosis of left ventricular dysfunction and congestive heart failure. The purpose of this study was to determine the values of serum NT-proBNP in normal Thai subjects compared with subjects from other countries. The design is a cross sectional study. The authors enrolled 243 consecutive healthy subjects (134 males and 109 females) from the checkup department of Bangkok Hospital for NT-proBNP measurement. The serum fraction was measured for NT-proBNP concentration by using Elecsys 2010 (Roche Diagnostics, Switzerland). The concentrations of NT-proBNP in normal Thai subjects were 33.30 $\pm$ 35.43 pg/ml. The NT-proBNP levels increased with age (age $\leq$ 50 years = 27.56 $\pm$ 28.77 pg/ml and age > 50 years = 47.20 $\pm$ 45.18 pg/ml, $p < 0.001$). Females usually have higher NT-proBNP than males (females = 40.42 $\pm$ 31.59 pg/ml, males = 27.51 $\pm$ 37.40 pg/ml, $p = 0.0045$). This study established the NT-proBNP concentrations in normal Thai subjects, which were not different from other studies. The authors suggested the normal cut-off values for subjects aged $\leq$ 50 years should be 100 pg/ml and the normal cut-off values for subjects aged > 50 years should be 200 pg/ml. The NT-proBNP assay could be used as a rule out marker for heart failure in patients and may trigger further cardiac investigation.

Key word : Normal Thai Subjects, NT pro-BNP, Age, Sex

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Congestive heart failure (CHF) is one of the major causes of morbidity and mortality in Thailand. It is primarily a disease of the elderly. In general practice heart failure is commonly misdiagnosed[1, 2]. The symptoms are non-specific and the clinical signs, although reasonably specific, are not at all sensitive. Consequently, even experienced physicians disagree on the diagnosis in individual cases, especially when the heart failure is mild[3]. Two studies in primary care have shown that many patients with breathlessness thought to have mild heart failure have been misdiagnosed[4,5]. The simplest confirmation of the diagnosis is provided by echocardiography, which is as reliable as other diagnostic methods such as radionuclide angiography. However, it is not readily available to general practitioners and precise measurement of left ventricular function is possible in only 58 per cent of patients because of obesity or pulmonary diseases. Recently, measurement of serum brain natriuretic peptide (BNP) levels has been suggested as a method of screening for left ventricular (LV) dysfunction[6-12]. The NT-proBNP, comprising 108 amino acids, is secreted mainly by the ventricle and in this process is cleaved into physiologically active BNP (77-108 amino acids) and the N-terminal fragment of proBNP (1-76 amino acids). In the pathophysiology of congestive heart failure (CHF), BNP participates in adaptive responses to hemodynamic alterations of heart failure[13,14]. The increased BNP level in patients with LV dysfunction has generated considerable interest in its diagnostic and prognostic properties in CHF patients. The purpose of this study was to determine the concentrations of NT-proBNP in normal Thai subjects and to compare them with subjects from other countries.

MATERIAL AND METHOD

The hospital ethical committee approved the study. The authors enrolled 243 consecutive healthy subjects (134 males and 109 females, age range: 16-87 years, mean: 42.8 years) who presented for their annual checkup and had no history of any cardiovascular, respiratory illness and other risk factors for CHF. Informed consents were obtained from all subjects.

Serum NT-proBNP assay

Blood samples were taken and centrifuged within 30 minutes. The serum fraction was separated and stored at -20°C until analysis. Serum NT-proBNP concentrations were measured by using Elecsys 2010 proBNP reagent kit (Roche Diagnostics, Switzerland). Elecsys proBNP reagent contains polyclonal antibodies that recognized epitopes located in the N-terminal part of proBNP. The total coefficient of variation (within run and between run) of our laboratory was less than 5 per cent.

Statistical analysis

All data were presented as the mean ± SD or percentage as appropriate. Categorical variables were compared by using chi-square test; continuous variables were compared by using independent student *t*-test or ANOVA. A two tailed p-value < 0.05 was considered significant. Statistical analysis was performed using SPSS version 10.0.

RESULTS

Serum NT-proBNP concentrations in 243 healthy subjects ranged between 5.00 and 272.70 pg/ml (mean: 33.30 ± 35.43 pg/ml). The 95th percentiles of NT-proBNP for all subjects, males and females were 104.16, 102.29, and 103.60 pg/ml respectively. The mean and standard deviation of serum NT-proBNP levels with different age and sex are shown in Table 1. Serum NT-proBNP levels in females were significantly higher than in males (p = 0.0045) and in age ≤ 50 years were significantly lower than in age > 50 years (p < 0.0001, Fig. 1). Fig. 2 shows the bar chart of NT-proBNP concentrations compared with males and females in different age groups. Fig. 3 shows the correlation between NT-proBNP and increasing age.

Table 1. Serum NT-proBNP concentrations with different age and sex.

	Sex ≤ 50 years (pg/ml)		n	> 50 years (pg/ml)		n	All (pg/ml)		n
	mean ± SD	95th		mean ± SD	95th		mean ± SD	95th	
Females	36.26 ± 24.59	85.18	81	52.44 ± 44.69	141.85	28	40.42 ± 31.59	103.60	109
Males	19.81 ± 30.09	79.99	91	43.79 ± 45.69	135.17	43	27.51 ± 37.40	102.29	134
All	27.56 ± 28.77	85.10	172	47.20 ± 45.17	137.54	71	33.30 ± 35.43	104.16	243

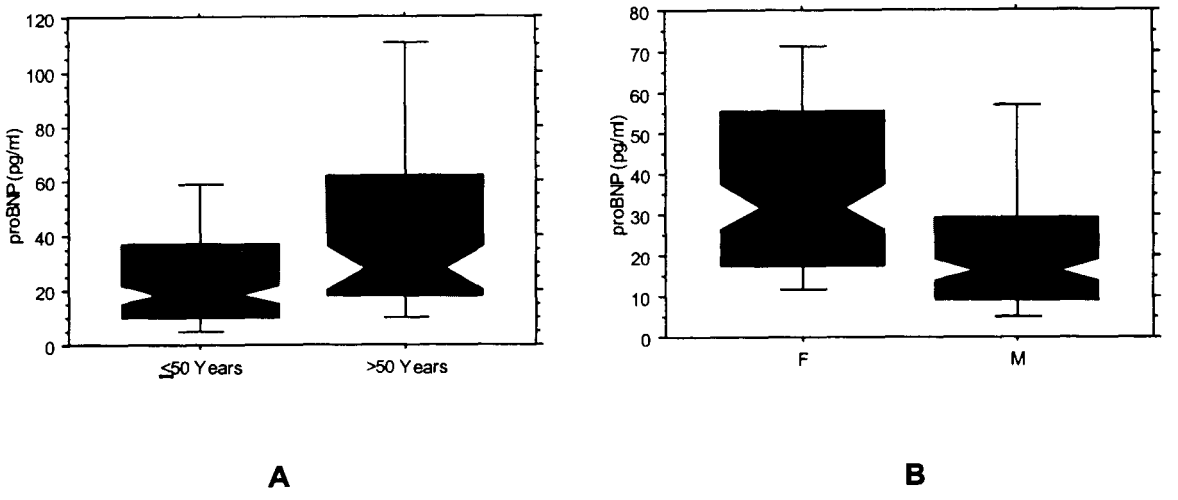

Fig. 1. **Box plot of NT-proBNP compares between A) males and females B) aged ≤ 50 years and aged > 50 years.**

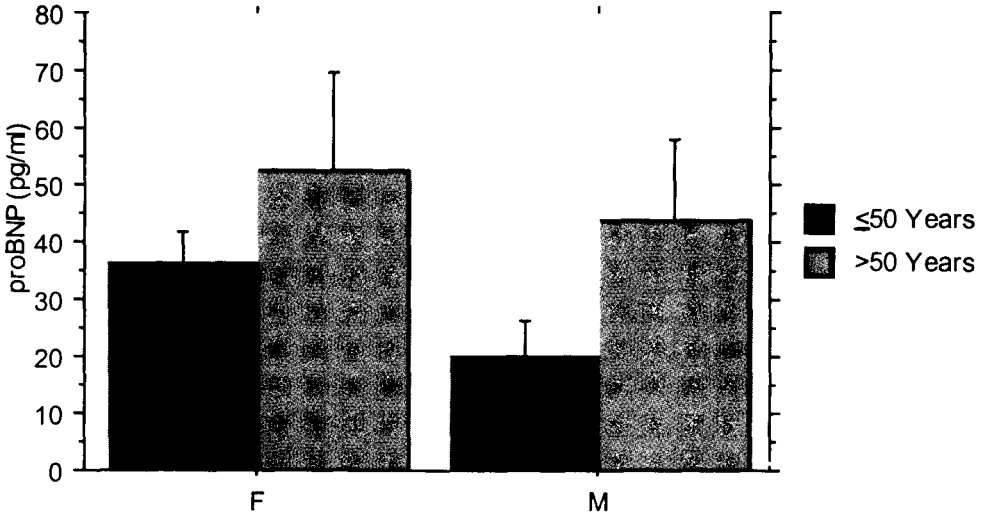

Fig. 2. **Bar chart of NT-proBNP compares males and females of different age groups.**

DISCUSSION

Although several studies on assays for BNP in select patient groups have been published, there is little data on the performance characteristics of an assay for NT-proBNP especially in Asian Countries (6,10,15-18). The serum NT-proBNP, with no known biological function, has been found to circulate at higher concentrations than BNP and may represent cardiac status over longer periods. This assay was easy to perform by a fully automated instrument and the serum sample did not need any additive substance. This high stability in whole blood allows the office-based physician to draw blood and send it to the reference laboratory for NT-proBNP measurement without the need for special precautions(13,19,20).

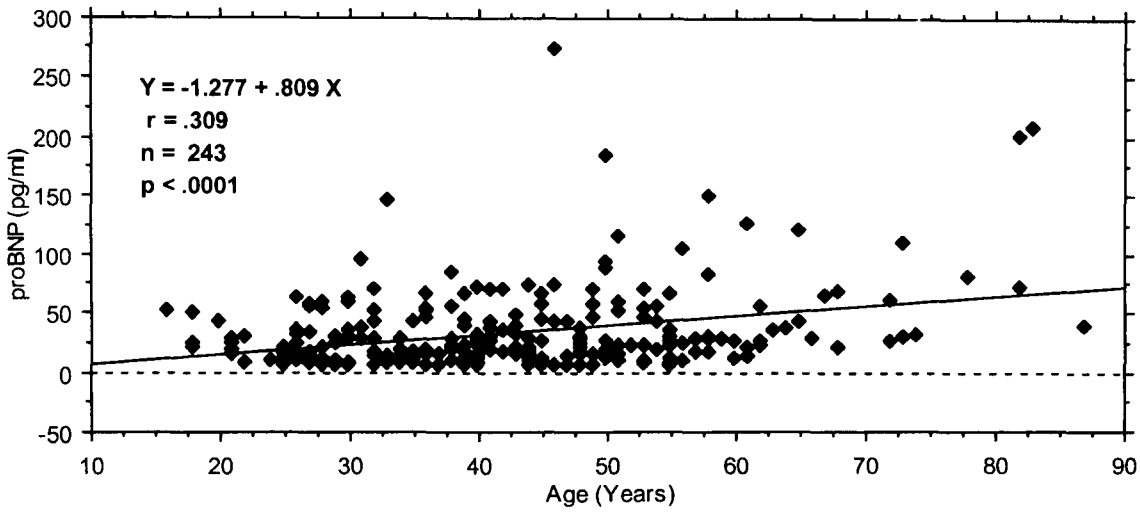

Fig. 3. Correlation of serum NT-proBNP with increasing age.

When the authors compared the results with the results from other investigators it was found that these finding were consistent with previous observations. In the year 2000, Smith et al reported the cut-off point of 158.2 pg/ml of BNP to rule out left ventricular systolic dysfunction from normal healthy subjects with a 92 per cent sensitivity[21]. From the study of Hobbs et al in 2002, the cut-off values for diagnosis of heart failure was 304.5 pg/ml of NT-proBNP with 100 per cent sensitivity, 70 per cent specificity, 7 per cent positive predictive value and 100 per cent negative predictive value[22]. Maisel et al demonstrated that the diagnosis accuracy of BNP at a cut-off of 100 pg/ml was 83.4 per cent. Negative predictive value of BNP at levels of less than 50 pg/ml was 96 per cent[15]. From our point of view, it is suggested that the cut-off value for both males and females aged $\leq$ 50 years should be 100 pg/ml and the cut-off value for both males and females aged > 50 years should be 200 pg/ml. These cut-off values may be suitable for Thai subjects to rule out heart failure patients from normal healthy persons particularly in a community setting. The very high negative predictive values and corresponding low likelihood ratios of a negative result suggest that this assay would be used only to rule out or as an exclusion test. Elevated concentrations of NT-proBNP should, therefore, trigger further cardiac investigation. Moreover, an NT-pro BNP measurement obtained within 1 or 2 hours may be useful in establishing or excluding the diagnosis of heart failure in patients with acute dyspnea.

SUMMARY

Serum concentrations of NT-proBNP could be used effectively as an initial test in a community screening programme and possibly, using the cut-off point, as a means of ruling out heart failure.

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ซีรั่มเอ็นเทอร์มินัลโปรเบรนแนททรียูเรติกเป็บไทด์ (เอ็นที-โปรบีเอ็นพี) ในคนไทยสุขภาพดี

วัฒนา เลี้ยววัฒนา, พบ, จีระศักดิ์ สิริธัญญนนท์, พบ**, ยศวีร์ สุขุมาลจันทร์, พบ***, สมศักดิ์ ชัยศุภมงคลลาภ, พบ***, เสริมกิจ วัฒนวารุณ, พบ***, ภาณุ จิวะธนพร, วทบ****, จารุวรรณ คังคะเกตุ, วทม*****, นิธิ มหานนท์, พบ**, เกียรติชัย ภูริปัญโญ, พบ***

อมิโนเทอร์มินัลของโปรเบรนแนททรียูเรติกเป็บไทด์ (เอ็นที-โปรบีเอ็นพี) สามารถนำมาใช้ในการตรวจคัดกรองให้การวินิจฉัย และพยากรณ์ โรคการทำงานหัวใจห้องซ้ายผิดปกติและโรคหัวใจล้มเหลวได้ดี แต่เนื่องจากข้อมูลที่เกี่ยวข้องกับเอ็นที-โปรบีเอ็นพี ในประชากรไทยยังมีอยู่น้อยมากคณะผู้วิจัยจึงมีวัตถุประสงค์ที่จะศึกษาถึงระดับ เอ็นที-โปรบีเอ็นพี ในประชากรไทยเพื่อเปรียบเทียบกับประชากรในประเทศอื่น ๆ และเพื่อเป็นข้อมูลพื้นฐานสำหรับประเทศไทยอีกด้วย คณะผู้วิจัยได้ทำการศึกษาผู้ที่มีสุขภาพดีที่มาตรวจเช็คร่างกายประจำปีที่หน่วยตรวจสุขภาพ โรงพยาบาลกรุงเทพจำนวน 243 ราย (ชาย 134 รายและหญิง 109 ราย) ซีรั่ม เอ็นที-โปรบีเอ็นพี ตรวจโดยใช้เครื่อง อิเล็คซีส 2010 (โรช ไดแอ็กโนสติกส์, สวิสเซอร์แลนด์) พบว่า ค่าซีรั่ม เอ็นที-โปรบีเอ็นพี เพิ่มสูงขึ้นตามอายุที่เพิ่มขึ้น (อายุน้อยกว่าหรือเท่ากับ 50 ปี = 27.56 $\pm$ 28.77 pg/ml และอายุมากกว่า 50 ปี = 47.20 $\pm$ 45.18 pg/ml, $p < 0.0001$) เพศหญิงจะมีค่าซีรั่ม เอ็นที-โปรบีเอ็นพี สูงกว่าในเพศชาย (เพศหญิง = 40.42 $\pm$ 31.59 pg/ml ส่วนเพศชาย = 27.51 $\pm$ 37.40 pg/ml, $p = 0.0045$) จากการศึกษาในครั้งนี้พบว่าค่าซีรั่ม เอ็นที-โปรบีเอ็นพี ในคนไทยไม่แตกต่างกับในประชากรประเทศอื่นโดยควรใช้ค่า cutoff สำหรับผู้ป่วยที่มีอายุน้อยกว่าหรือเท่ากับ 50 ปีที่ 100 pg/ml และสำหรับผู้ป่วยที่มีอายุมากกว่า 50 ปีที่ 200 pg/ml โดยควรใช้ค่าซีรั่ม เอ็นที-โปรบีเอ็นพี ในการ rule out สำหรับผู้ป่วยหัวใจวายในการดูแลรักษาแบบชุมชนและจะเป็นสิ่งกระตุ้นให้ทำการค้นหาสาเหตุของภาวะหัวใจวายต่อไป

คำสำคัญ : ประชากรไทยปกติ, เอ็นที-โปรบีเอ็นพี, อายุ, เพศ

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