N-Terminal Probrain Natriuretic Peptide (NT-proBNP) in the Diagnosis of Heart Failure in Patients with Acute Dyspnea

Adisak Maneesai, MD., Rungroj Krittayaphong, MD.
Division of Cardiology, Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand

Abstract

Objective: To validate the level of NT-pro BNP in the diagnosis of heart failure in patients presenting with acute dyspnea to the emergency department of Siriraj hospital.

Background: The utility of aminoterminal pro-brain natriuretic peptide (NT-proBNP) testing in the emergency department to rule out acute congestive heart failure (CHF) and the optimal cut points in Thai patients have not been established yet. We conducted a prospective study of 100 patients who presented to the emergency department of Siriraj hospital with acute dyspnea. The clinical diagnosis of acute CHF was determined by two cardiologists who were blinded to NT-proBNP results. The main outcome was a comparison of NT-proBNP results with the clinical diagnosis made by cardiologists for identifying acute CHF.

Results: The mean age of patients in this study was 51.5 years (46% female and 37% male). The final diagnosis in 46% of patients was acute dyspnea due to heart failure. The mean value of NT-proBNP among the patients diagnosed with acute heart failure was 15,976 pg/ml versus 984 pg/ml in the patients without heart failure (p<0.001). A NT-proBNP at cutoff point of 1,789 pg/ml was highly sensitive and specific for diagnosis of heart failure. The sensitivity of NT-proBNP at a cutoff level of 1,789 pg/ml was 94%, with a specificity of 90%, a negative predictive value of 93.5 % and a positive predictive value of 96.2%.

Conclusion: NT-proBNP measurement in addition to clinical information is useful for the diagnosis and exclusion of acute heart failure in patient presenting with acute dyspnea in the emergency department setting.

Introduction

Heart failure is a common diagnosis among patients presenting with acute dyspnea. Heart failure is often difficult to diagnose in the emergency department and in urgent care settings. The current diagnosis of heart failure is based on medical history and physical examination with further confirmation by other tests. Clinical misdiagnosis of heart failure in emergency department is common especially when the clinical manifestations are mild. Brain natriuretic peptide (BNP) is a neurohormone secreted by both atrial and ventricular myocytes. Most BNP however is produced in the cardiac ventricles in response to volume expansion and pressure overload. BNP is produced by the cleavage of a precursor protein (proBNP) into the biologically inactive peptide NT-proBNP, and BNP which produces natriuresis, diuresis, vasodilatation and smooth muscle relaxation (1). More recently, blood tests to measure the levels of B-type Natriuretic peptide and N-terminal natriuretic peptide have been used to aid in the diagnosis of heart failure (2-4). Plasma BNP and NT-proBNP are raised in patients with heart failure and have been used to establish or rule out the diagnosis of heart failure. Plasma BNP and NT-proBNP concentrations are known to be affected by age, sex and race (4). Whether measurement of NT-proBNP is equivalent to measurement of BNP for diagnosis of heart failure is currently uncertain (5).
The objectives of this study were 1) to validate the level of NT-pro BNP in the diagnosis of heart failure in patients at Siriraj hospital who presented with acute dyspnea and 2) to evaluate the sensitivity and specificity of NT-proBNP in the diagnosis of heart failure in patients presenting to the emergency department with acute dyspnea.

**Methods**

**Study design**

The study was a prospective study conducted in the emergency department at Siriraj hospital. The patients were evaluated by physicians in the emergency department. The patients’ treatment in the emergency department was not affected by the study test results. The study protocol was approved by the Siriraj ethical committee.

**Study population**

The number of the patients that should be included in this study (for 95%CI, sensitivity 80%, specificity 80%, variation 12%) was calculated by Nquery advisor 3.0 to be eighty six patients. A total of 100 patients were enrolled in the study.

**Inclusion criteria:** Patients over the age of 18 years were eligible for enrollment if they presented to the emergency department with acute dyspnea and they were able to give a blood sample within 8 hours of arrival.

**Exclusion criteria:** Exclusion criteria were as follows: patients under 18 years of age, pregnancy, renal failure (defined as serum creatinine > 2.0 mg/dl), acute coronary syndrome unless the predominant symptom at presentation was dyspnea, acute asthma unless a diagnosis of heart failure was suspected, (asthma was defined as having a past history of asthma, and presenting with dyspnea due to bronchospasm that promptly responded to bronchodilator), obvious traumatic causes of dyspnea, cardiogenic shock, and patients who requested transfer to another hospital.

**Data collection**

Written informed consent was obtained in every patient. Blood samples were collected for measurement of BNP and NT-proBNP. The medical residents in the emergency department formulated a heart failure or not-heart failure diagnosis based on history and physical examination. The probability that the patient had congestive heart failure by assigning a point in a scale ranging from 0-100 percent clinical certainty was also evaluated.

The author (A.M.) collected the data, including demographic data, medical history, physical examination and the results of blood tests from the medical records. An echocardiogram was encouraged in hospital if the patient was admitted.

**Determination of diagnosis**

To determine the actual diagnosis, two cardiologists reviewed all medical records of each patient and independently classified the diagnosis as dyspnea due to congestive heart failure, acute dyspnea due to non-cardiac causes in a patient with a history of left ventricular dysfunction, or dyspnea not due to congestive heart failure.

The two cardiologists were blinded to the B-type natriuretic peptide and NT-pro BNP levels as well as to the emergency department physicians’ diagnosis. They were able to access the emergency department data sheets and any additional information that became available after evaluation in the emergency department. This information included the chest roentgenogram; medical history obtained from medical charts not available to the emergency department physicians at the time of presentation; the results of subsequent tests, such as echocardiography, radionuclide angiography, or left ventriculography- performed at the time of cardiac catheterization; and the hospital course for patients admitted to the hospital. The principles for diagnosis of heart failure contained in the European Society of Cardiology guidelines were followed, and all patients with heart failure fulfilled Framingham congestive heart failure score criteria (6).

For patients with a diagnosis other than congestive heart failure, confirmation of a non-cardiac cause was done on the basis of the following observations: normal chest roentgenogram (absence of heart enlargement and pulmonary venous hypertension); roentgenographic signs of chronic obstructive lung disease, pneumonia, or lung cancer; normal heart function according to echocardiography, radionuclide ventriculography, or left ventriculography performed at the time of cardiac catheterization; abnormal pulmonary function test results or follow-
up results in the pulmonary clinic; response to treatment with nebulizers, corticosteroids, or antibiotics from the emergency department or hospital; and the absence of admission to the hospital for congestive heart failure over the following 30 days. In all cases of congestive heart failure, the two cardiologists were asked to agree on the severity according to the New York Heart Association class.

**Measurement of NT-proBNP**

During initial evaluation at the emergency department, when undergoing venipuncture for routine blood tests, a 5-ml specimen of venous blood was collected in EDTA tubes for assay of NT-proBNP. The time of blood collection was recorded.

NT-proBNP was measured with the use of an electrochemiluminescence immunoassay (Elecsys proBNP, Roche). The coefficient of variation within a given assay for levels of 350, 8700 and 13 000 pg per milliliter was 1.0 to 2.5 percent (7)

**Main outcome**

Receiver-operating characteristic curves were used to evaluate the value of NT-proBNP in the diagnosis of heart failure. Area under the curve was then calculated. The sensitivity and specificity of NT-proBNP testing was examined at various levels of NT-proBNP. The optimum cutoff point value was determined at the best sensitivity and specificity.

**Statistical analysis**

Comparison of NT-proBNP among various diagnosis groups was performed using the t-test for independent samples. We evaluated the value of NT-proBNP in the diagnosis of heart failure, comparing sensitivity, specificity and accuracy with individual clinical findings.

To determine the capacity of NT-proBNP levels to differentiate heart failure from other causes of dyspnea, we used receiver-operating characteristic curve analysis to illustrate various cutoff values of NT-proBNP for sensitivity, specificity, positive and negative predictive value, overall accuracy of the test and area under the receiver-operating characteristic curves. The optimum cutoff point value was determined at the best sensitivity and specificity. P value <0.05 was considered statistically significant.

**Results**

One hundred eligible patients were enrolled. Of the one hundred patients in the study 54% had a final diagnosis of acute congestive heart failure (CHF) and 46 % had noncardiac dyspnoea. A comparison of clinical characteristics at presentation between patients who had heart failure and those who did not are presented in Table 1.

**Table 1. Baseline characteristics of patients with acute dyspnea**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Acute HF (n = 46)</th>
<th>No HF (n = 54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.7 ± 24.5</td>
<td>49.7 ± 24.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex: male</td>
<td>46</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>DM</td>
<td>7</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>HT</td>
<td>33</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Positive troponin T</td>
<td>35</td>
<td>28</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Clinical diagnosis**

Various etiologies of dyspnea in patients who did not have heart failure are shown in Figure 1. Many patients were discharged from the emergency department without a definite diagnosis.

**Figure 1.** Diagnoses among patients who did not have acute heart failure.

**NT-proBNP results**

Mean NT-proBNP levels among patients with acute heart failure and without acute heart failure are shown in Figure 2. Among patients with
acute heart failure, the mean NT-proBNP level was 15967 ± 12356 pg/ml compared with 984 ± 3082 pg/ml in patients without heart failure (p<0.001).

Figure 2. Mean NT-proBNP levels among patients with and without heart failure. P<0.001.

Median NT-proBNP levels among patients who with acute heart failure and those without are shown in Figure 3. Among patients with acute heart failure, the mean NT-proBNP level was 11,944 pg/ml (25th and 75th percentile were 4,147 and 28,302 pg/ml) compared with 377 pg/ml (25th and 75th percentile were 104 and 970 pg/ml) among patients without heart failure.

The NT-proBNP level was an accurate diagnostic test for diagnosis of heart failure. Receiver-operating characteristics analyses (Figure 4) demonstrated the NT-proBNP to be highly sensitive and specific as indicated by an area under the receiver-operating characteristic curve of 0.96 (p<0.001). The optimal cutoff point was tested and a NT-proBNP cutoff level of 1,789 pg/ml was calculated to have a sensitivity of 94%, a specificity of 90%, a negative predictive value of 93.5% and a positive predictive value of 96.2%. (Table 2)

Table 2. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) when using NT-proBNP cutoff level at 1,789 pg/ml for ruling in and ruling out heart failure

<table>
<thead>
<tr>
<th></th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>94%</td>
</tr>
<tr>
<td>Specificity</td>
<td>90%</td>
</tr>
<tr>
<td>PPV</td>
<td>96.2%</td>
</tr>
<tr>
<td>NPV</td>
<td>93.5%</td>
</tr>
</tbody>
</table>

Discussion

Our findings validated the use of NT-proBNP testing as an aid in the diagnosis of heart failure. The use of NT-proBNP in the diagnosis of heart failure has been evaluated in previous larger studies and the optimal cutpoint was significantly lower than this study (<900 pg/ml). (8-10) These studies used clinical judgement as a gold standard for the diagnosis of heart failure and focused on the exclusion of heart failure. This may have resulted in a lower cut point value thereby attaining a higher specificity for the test. This study, when using a higher cut point, found that NT-proBNP could be of use for making the diagnosis of acute heart failure with a demonstrated by high sensitivity and specificity.
NT-proBNP was highly sensitive and specific for the diagnosis of acute heart failure with a highly significant area under the curve (AUC=0.96) \( p<0.001 \)

Clinical judgment for diagnosis using history and physical examination when made in the emergency department is often inadequate. This study showed that the recognition of third and fourth heart sound was usually omitted in the routine emergency room assessment of patients with acute dyspnoea. Previous observations have found that a good initial physical assessment alone can have a sensitivity and specificity for diagnosis of heart failure of about 60-70 percent. When initial clinical judgement was done in emergency department, the correct diagnoses are often missed.

Unlike acute coronary syndromes, in which cardiac markers such as troponin and creatinin kinase can establish the diagnosis and have worldwide generally accepted specific cutoff values, NT-proBNP does not have a widely-accepted cutoff value. Previous studies have demonstrated the relation of BNP and NT-proBNP level with the severity of heart failure. This may have resulted in different cutoff values for NT-proBNP in different studies. In this study conducted in Siriraj hospital, we found that level of NT-proBNP in those with acute heart failure was significantly higher than in the PRIDE study. This could be due to different groups of patient or a different level of severity of heart failure. In Thailand, the patients who present at tertiary hospitals, like Siriraj hospital, with acute heart failure tend to have severe heart failure which can result in higher NT-proBNP levels.

In conclusion, this study in a single center hospital demonstrated that NT-proBNP could be used in combination with clinical judgment for making the diagnosis of heart failure and also ruling out heart failure. The optimal cutoff point in this study was 1,789 pg/ml. This finding is based on the clinical situation in which the diagnosis of heart failure is not clinically straightforward. Our suggestion is that in Thailand this test would be most useful where the diagnosis is unclear. Where the diagnosis of heart failure is straightforward, we feel this diagnostic test should not be performed routinely because it will result in higher costs. We caution also that the diagnosis of heart failure should not be based on laboratory testing alone without using the clinical background.

References

การใช้ N-terminal Probrain Natriuretic Peptide (NT-proBNP) ในการวินิจฉัยภาวะหัวใจสั่นไหวในผู้ป่วยมีฝีมือของการหอบเหนื่อยเฉียบพลัน

ธิดาศิลป์ ผึ้งไฮ, ผศ., รุ่งโรจน์ ภูคุณพงษ์, ผศ.
สถาบันวิจัย, ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ศิริราชพยาบาล

บทคัดย่อ

วัตถุประสงค์: การศึกษานำการศึกษาระดับ NT-proBNP เพื่อหาค่าที่เหมาะสมในการวินิจฉัยภาวะหัวใจสั่นไหวในผู้ป่วยที่มีฝีมือของการหอบเหนื่อยเฉียบพลัน

วิธีการศึกษา: การศึกษาเกิดในผู้ป่วยของโรงพยาบาลศิริราชที่มีฝีมือของการหอบเหนื่อยเฉียบพลัน ผู้ป่วยจะได้รับการฉีดยาเพื่อวัดค่า NT-proBNP หลังจากนั้นผู้ป่วยจะได้รับการวินิจฉัยชั้นสุดท้ายจากอายุรแพทย์โรคหัวใจว่าอาการหอบเหนื่อยเกิดจากภาวะหัวใจสั่นไหวหรือไม่ การศึกษานี้จะทำการเปรียบเทียบค่า NT-proBNP กับการวินิจฉัยระยะหัวใจสั่นไหวทางคลินิก

ผลการศึกษา: ผู้ป่วยที่มีฝีมือของการหอบเหนื่อยเฉียบพลันและเจ้าสุ่มศึกษามีอายุเฉลี่ย 51.5 ปี โดยมี 46% เป็นเพศผู้หญิงและ 37% เป็นเพศชาย ผู้ป่วยที่มีฝีมือในการวินิจฉัยในชั้นสุดท้ายวัดจากภาวะหัวใจสั่นไหวเป็น 46%. การศึกษาพบว่าค่า NT-proBNP ในผู้ป่วยที่มีฝีมือของการหอบเหนื่อยเกิดจากภาวะหัวใจสั่นไหวของผู้ป่วย NT-proBNP 984 pg/ml (p<0.001) ค่าการวินิจฉัยทางสถิติพบว่ามีค่าที่ NT-proBNP ที่มากกว่า 1,789 pg/ml เป็นตัวคัดเลือกผู้ป่วยมีภาวะหัวใจสั่นไหว โดยความถี่ sensitivity 94%, specificity 90%, negative predictive value 93.5% และ positive predictive value 96.2%

สรุป: การใช้ NT-proBNP ในการวินิจฉัยภาวะหัวใจสั่นไหวในผู้ป่วยที่มีฝีมือของการหอบเหนื่อยเฉียบพลันเป็นการทดสอบที่มีประโยชน์และมีความจำเป็นทางคลินิกสูง