

Original Article

Diagnostic values of NT-proBNP in acute dyspnea among elderly patients

Qin Su^{1*}, Hongsheng Liu^{1*}, Xian Zhang¹, Wei Dang¹, Runmei Liu², Xiaodong Zhao¹, Xiaoling Yuan¹, Yuhong Qin¹, Jianbo Zhang¹, Chunming Chen¹, Yunfeng Xia²

Departments of ¹Emergency, ²Geriatric Cardiology, The First Affiliated Hospital of PLA General Hospital, Beijing 100048, China. *Co-first authors.

Received July 7, 2015; Accepted August 21, 2015; Epub October 1, 2015; Published October 15, 2015

Abstract: The study aims to evaluate a rapid testing of NT-proBNP in differential diagnosis of cardiac and pulmonary dyspnea among elderly emergency patients. Two hundred sixty-eight dyspnea patients with ages of ≥ 60 years old participated in the study. Based on their clinical diagnosis, the patients were divided into three groups: group A diagnosed with pulmonary dyspnea (PD), group B diagnosed with congestive heart failure (CHF), and group C diagnosed with combined dyspnea (CHF+PD). NT-proBNP levels among the three groups were compared. NT-proBNP levels in group A were significantly lower than those in groups B and C. No significant difference was observed between groups B and C in terms of NT-proBNP levels ($P > 0.05$). Our data showed that NT-proBNP levels in patients with cardiac dyspnea were significantly higher than those in patients with pulmonary dyspnea. Person linear association analysis revealed that NT-proBNP levels were reversely associated with LVEF ($r = -0.675$, $P < 0.01$), indicating that higher NT-proBNP levels result in lower LVEF and poorer heart functions. NT-proBNP is a valuable biomarker in differential diagnosis of pulmonary and cardiac dyspnea among elderly patients due to the high sensitivity of the testing method and the strong association with the severity of heart failure.

Keywords: Amino-terminal pro-B-type natriuretic peptide, emergency, elderly patients, dyspnea, biomarker

Introduction

Dyspnea is common among elderly patients who seek emergency medical care. Given that the two major types of dyspnea, namely, cardiac and pulmonary dyspnea, have similar clinical presentations but require different treatments, any delayed diagnosis and treatment may result in increased rates of disability and mortality among patients. Elderly patients often have combined medical conditions that involve multiple organs and systems, such as heart failure-induced pulmonary dysfunctions or vice versa. Complications present an additional challenge for emergency room physicians in conducting differential diagnosis and treatment that are essential for the survival of the patients.

Initial clinical evaluations that are based on symptoms, physical signs, and chest radiography remain inconclusive in assessing many patients with acute dyspnea. Bedside Doppler echocardiography is a reliable and non-invasive method that offers additional diagnostic infor-

mation for initial clinical evaluations. A major advancement in medicine over the past decade has been the discovery and the development of novel biomarkers that are aimed at improving the ability of clinicians to perform a diagnosis and to predict the prognosis of their patients. Many surveys have identified the important role of BNP in the differential diagnosis of patients with acute dyspnea and the close association of its level to the severity of heart failure [1, 2]. BNP is composed of 32 amino acids and is produced as a pre-prohormone protein, proBNP. In response to myocardial stretch, volume overload, and elevation of end-diastolic pressure, proBNP is secreted from cardiac myocytes and cleaved into an active BNP and an inactive N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is composed of 76 amino acids. As both are biologically distinct, BNP and NT-proBNP are usually used in the assessment of cardiac functions and have an important role in the regulation of natriuresis, diuresis, and vascular tone [3-7]. ACC/AHA guidelines recommend the use of BNP and NT-proBNP for the

Diagnosis of dyspnea among elderly

exclusive diagnosis of heart failure [8]. BNP and NT-proBNP testing is a very valuable diagnostic and prognostic tool for heart failure [9]. NT-proBNP, which has a longer half-life and a more consistent blood concentration than BNP, is indicated by recent data as a better marker in detecting the early stage of a heart failure [10]. In this study, we evaluated a rapid NT-proBNP testing among 268 elderly patients who suffered acute dyspnea. The goal of the evaluation was to determine the diagnostic value of NT-proBNP in differential diagnosis between cardiac and pulmonary dyspnea.

Materials and methods

Subjects

We retrospectively analyzed 268 cases of acute dyspnea among elderly patients admitted into the emergency room from June 2010 to June 2012. Patients who had dyspnea caused by trauma, pericardial tamponade, or acute coronary artery syndrome were excluded from the study, as well as those with renal failure, ascites caused by cirrhosis, or thyroid diseases. All patients were 60 years old or older, with an average age of 74.1 ± 7.9 yr. A total of 151 male and 117 female patients participated in the study. In addition to the routine blood testing, blood biochemistry, blood gas analysis, and electrocardiography, measurement of blood NT-proBNP levels was performed within 30 minutes after patient admission. Bedside echocardiography, left ventricular ejection fraction (LVEF) measurement, and X-ray radiography were performed within an hour after patient admission. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of General Hospital of PLA. Written informed consent was obtained from all participants.

Classification

Patients were divided into three groups based on their underlying diseases. Group A consisted of 90 cases of dyspnea associated with pulmonary diseases (PD), which comprised 27 cases of acute onset of chronic obstructive pulmonary disease (COPD), 18 cases of acute bronchial asthma attack, 12 cases of bronchiectasis with infection, 10 severe cases of pneumonia, 8 cases of interstitial lung disease, 8

cases of massive pleural effusion, and 7 cases of pneumothorax. Group B consisted of 113 cases of dyspnea resulting from chronic heart failure (CHF), which comprised 45 cases of coronary heart disease, 21 cases of hypertensive heart disease, 16 cases of post percutaneous coronary intervention (PCI), 13 cases of dilated cardiomyopathy, 12 cases of rheumatic heart disease, and 6 cases of hypertrophic cardiomyopathy. Group C consisted of 65 cases of dyspnea caused by the combination of CHF and PD. All patients in this group possessed a history of PD and heart failure. Among these patients were 28 cases of acute heart failure (AHF) caused by infections, 27 cases of CHF, and 20 cases of pulmonary heart disease. Levels of NT-proBNP were compared among these three groups. The subjects were also classified in the study based on the similarity of their profiles, specifically according to age and sex, and the severity of their dyspnea was assessed.

CHF was diagnosed based on Framingham Standards, color Doppler echocardiography, chest X-ray, and patient responsiveness to drug treatments. The heart functional classification was based on the guideline of the American Heart Association-NYHA functional classification system. In groups B and C, 142 patients of Class II or above, composed of 66 patients of Class II, 47 patients of Class III, and 29 patients of Class IV, were identified. Relationships between their NT-proBNP levels, degrees of heart failure, and LVEF were compared.

Testing methods

After the patients were admitted into the hospital, 2 ml of their blood was collected in a VACUETTE EDTA K2 tube. NT-proBNP measurements were performed using the Canada RAMP NT-proBNP Assay. Blood samples were then loaded onto the machine and measurements were performed according to the instructions of the manufacturer. The machine measured NT-proBNP in the range of 5 ng/L to 35,000 ng/L.

Statistical analysis

Data were statistically analyzed using SPSS-13.0 software. Means and standard deviation (SD) were determined. Means of different groups were analyzed through one-way ANOVA,

Diagnosis of dyspnea among elderly

Table 1. NT-proBNP levels and LVEF values in patients with different levels of heart classification

NYHA Classification	N	NT-proBNP (ng/L)	LVEF (%)
Class II	66	531.42±96.15	58.5±8.1
Class III	47	2675.38±84.96	47.1±7.5
Class IV	29	5723.84±135.23	40.3±6.8

Note: two-group comparison among groups of NYHA Class II, III and IV. $P < 0.01$.

while multiple comparisons between groups were analyzed using the *F*-test. Relationships were determined by person association analysis. Statistical significance was identified at $P < 0.05$.

Results

Plasma NT-proBNP levels

Our data showed that NT-proBNP levels in group A were significantly lower than those in groups B and C [(186.4±69.5) vs. (1739.2±771.5) and (1837.4±874.6) ng/L, $P < 0.01$]. No statistical difference was observed between groups B and C in terms of blood NT-proBNP levels ($P > 0.05$). NT-proBNP levels among patients with cardiac dyspnea were significantly higher than those among patients with only pulmonary dyspnea.

Relationships between NT-proBNP levels, NYHA classification, and LVEF

Among the patients in groups B and C, the levels of heart functional classification (Classes II, III, and IV) were positively related to NT-proBNP levels ($P < 0.01$, **Table 1**). In other words, higher NT-proBNP levels were related to higher heart functional classes. Person linear association analysis showed that NT-proBNP levels were reversely related to values of LVEF. These results indicated that high NT-proBNP level is related to low LVEF value and poor cardiac function.

NT-proBNP testing

The positive predictive value of >600 ng/L was used in the differential diagnosis. In group A that comprised 90 pulmonary dyspnea patients, 74 had blood NT-proBNP levels that were lower than 600 ng/L and 16 had levels above 600 ng/L. In group B that comprised 113 cardiac dyspnea patients, 104 had NT-proBNP levels above 600 ng/L and the rest (9

patients) had NT-proBNP levels lower than 450 ng/L. Using elevated plasma NT-proBNP levels as an indicator to diagnose cardiac dyspnea, a sensitivity of 92.0%, a specificity of 82.2%, a positive predictive value of 86.7%, and a negative predictive value of 89.2% were obtained.

Discussion

Dyspnea, as a common clinical condition diagnosed in the emergency room, often has unknown specific causes and is frequently made complicated by other illnesses. Pulmonary and cardiac diseases are two major causes of dyspnea, which have high morbidity and mortality rates. Therefore, accurate diagnosis of dyspnea is essential to prescribe effective treatments and to achieve better patient outcomes. Echocardiography is the most common tool in evaluating the proper functioning of the heart. However, an expensive machine and specially trained physicians are required in implementing echocardiography. Since not many hospitals have such resources in their emergency departments, applications of echocardiography in an emergency setting are often limited. In addition, patients with mild heart failure or slightly higher ventricular tension may not show abnormalities in their echocardiography results. Among patients with severe heart failure or dyspnea, the accuracy of echocardiography may be significantly affected by the patient's body position during the examination. Therefore, a fast, specific, and sensitive method for differential diagnosis of dyspnea is important in managing the condition of patients and in reducing the mortality rate.

BNP is a peptide hormone secreted by ventricular cardiocytes in response to an increase in ventricular volume or pressure overload. The function of BNP includes the promotion of natriuresis and the inhibition of the sympathetic and renin-angiotensin-aldosterone system. BNP is largely produced from the left ventricle, although the right ventricle also produces a small amount of BNP. The level of BNP is an important factor for assessing heart failure and for improving patient outcomes [11]. Pro-BNP is initially produced in vivo. After entering the blood circulation, Pro-BNP is proteolytically processed to produce equal amounts of BNP and NT-proBNP. BNP performs a biological activity, while NT-proBNP does not. BNP has a shorter half-life of approximately 20 min. NT-proBNP has a relatively longer half-life of approximately

Diagnosis of dyspnea among elderly

two hours, and its level slowly increases in vitro and in vivo. NT-proBNP, which is metabolized in the kidney, is about four to six folds more stable than BNP, both in vitro and in vivo, and can be used as an indicator in monitoring changes in the left ventricle pressure and in the ventricular tension [12, 13]. Given its better stability and suitability for clinical application, NT-proBNP is gradually replacing BNP in recent years. O'Donnoghie et al. demonstrated that NT-proBNP has higher sensitivity and better correlation to the severity of heart failure than BNP [14].

According to the current guideline, NT-proBNP and BNP have an average role in the examination of heart failure [15, 16]. Mueller et al. indicated that BNP and NT-proBNP have an equivalent value in the diagnosis of heart failure [17]. In their study, BNP and NT-proBNP levels were determined among 251 dyspnea patients, whose heart failures were diagnosed based on the Framingham standard and echocardiography. Statistical analysis of the ROC curve revealed that areas under the curve for BNP and NT-proBNP were 0.916 and 0.903, respectively, demonstrating non-significance. Lainchbury et al. [18] found that among dyspnea patients, plasma NT-proBNP levels among patients with heart failure were significantly higher than those whose dyspnea was caused by other conditions. Our study proved that among elderly dyspnea patients, CHF and CHF+PD groups had significantly higher plasma NT-proBNP levels than those of the PD group. When the plasma NT-proBNP level was above the reference value of 600 ng/L, the sensitivity, specificity, positive predictive value, and the negative predictive value were 92.0%, 82.2%, 86.7%, and 89.2%, respectively, which conformed to published reports [19]. NT-proBNP levels among patients in Class IV were significantly higher than those among patients in Classes II and III. In addition, NT-proBNP was found reversely related to LVEF, as measured by echocardiography. Higher NT-proBNP was related to lower LVEF and poorer heart functions, which was consistent with the findings of Lainchbury et al. [18]. The increased NT-proBNP level indicated possible heart failure among patients, especially those who suffered from respiratory conditions. Since severe pulmonary infections often induce acute heart failure, heart failure can be difficult to detect by merely monitoring clinical symptoms. Measuring NT-proBNP is simple and quick and can be clinically

used as an important reference in differential diagnosis. In this study, we likewise proved that NT-proBNP levels were related to the clinical conditions of patients admitted into the emergency department. We measured NT-proBNP levels three days after patient admission. Among 76 CHF patients, the NT-proBNP level of 64 patients decreased significantly after their clinical conditions improved. Eleven patients exhibited an increase in their NT-proBNP levels as their conditions deteriorated, three of which eventually died. The data demonstrated that decreased NT-proBNP levels mark an improved patient's condition, whereas increased NT-proBNP levels suggest deterioration of the patient's condition and unfavorable outcomes. In the present study, 26 patients displayed normal echocardiography, but had elevated NT-proBNP. After treatment with combined medications that include digitalis and diuretics, the patients' conditions significantly improved and their NT-proBNP levels returned to normal. This observation suggests that NT-proBNP can be used to diagnose abnormalities of the heart structure and of dilation earlier than echocardiography among patients with no clinical symptoms. Furthermore, recent studies prove that NT-proBNP can be used to identify individuals who have no heart dysfunctions but have increased risks of cardiovascular diseases and death. Therefore, NT-proBNP is at present an important indicator in predicting patient outcomes.

Although NT-proBNP testing has high sensitivity and specificity in the diagnosis of heart failure, the level of heart failure can be affected by many factors such as age, renal function, race, and body mass. Similar with other diagnostic tests, NT-proBNP should be assessed along with patient history and physical examination. In addition, physicians should be aware of factors that may cause an increased level of NT-proBNP. When the NT-proBNP value is above the threshold, a possible heart failure should be considered. The negative predictive value of NT-proBNP is more significant. When NT-proBNP is lower than 300 ng/L, the negative predictive value is 98%, providing a strong possibility of heart failure. In summary, a rapid bedside testing of NT-proBNP can be used as a tool to facilitate differential diagnosis among patients with acute dyspnea. Consequently, the overall disease management and the treatments of these patients become more efficient and effective.

Diagnosis of dyspnea among elderly

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yunfeng Xia, Department of Geriatric Cardiology, The First Affiliated Hospital of PLA General Hospital, Beijing 100048, China. Tel: +86 10 88550172; E-mail: sqhscn@163.com

References

- [1] Karakiliç E, Kepez A, Abali G, Coşkun F, Kunt M and Tokgözoğlu L. The relationship between B-type natriuretic peptide levels and echocardiographic parameters in patients with heart failure admitted to the emergency department. *Anadolu Kardiyol Derg* 2010; 10: 143-149.
- [2] Mastandrea P. The diagnostic utility of brain natriuretic peptide in heart failure patients presenting with acute dyspnea: a meta-analysis. *Clin Chem Lab Med* 2013; 51: 1155-1165.
- [3] Jernberg T, Stridsberg M, Venge P and Lindahl B. N-terminal pro brain natriuretic peptide on admission for early risk stratification of patients with chest pain and no ST-segment elevation. *J Am Coll Cardiol* 2002; 40: 437-445.
- [4] Jernberg T, James S, Lindahl B, Johnston N, Stridsberg M, Venge P and Wallentin L. Natriuretic peptides in unstable coronary artery disease. *Eur Heart J* 2004; 25: 1486-1493.
- [5] Hall C. Essential biochemistry and physiology of (NT-pro) BNP. *Eur J Heart Fail* 2004; 6: 257-260.
- [6] Murray H, Clod B, Collier CP and Sivilotti ML. Potential impact of N-terminal pro-BNP testing on the emergency department evaluation of acute dyspnea. *CJEM* 2006; 8: 251-258.
- [7] Weber M and Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. *Heart* 2006; 92: 843-849.
- [8] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; American College of Chest Physicians; International Society for Heart and Lung Transplantation; Heart Rhythm Society. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation* 2005; 112: e154-235.
- [9] Palazzuoli A, Gallotta M, Quatrini I and Nuti R. Natriuretic peptides (BNP and NT-proBNP): measurement and relevance in heart failure. *Vasc. Health Risk Manag* 2010; 6: 411-418.
- [10] Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H and Takano T. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. *Eur J Heart Fail* 2004; 6: 295-300.
- [11] Kociol RD, Horton JR, Fonarow GC, Reyes EM, Shaw LK, O'Connor CM, Felker GM and Hernandez AF. Admission, discharge, or change in B-type natriuretic peptide and long-term outcomes: data from Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) linked to Medicare claims. *Circ Heart Fail* 2011; 4: 628-636.
- [12] Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG and Richards AM. Treatment of heart failure guided by plasma amino-terminal brain natriuretic peptide (N-BNP) concentrations. *Lancet* 2000; 355: 1126-1130.
- [13] Steiner J and Guglin M. BNP or NT-proBNP? A clinician's perspective. *Int J Cardiol* 2008; 129: 5-14.
- [14] O'Donoghue M, Chen A, Baggish AL, Anwaruddin S, Krauser DG, Tung R and Januzzi JL. The effects of ejection fraction on N-terminal ProBNP and BNP levels in patients with acute CHF: analysis from the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. *J Card Fail* 2005; 11: S9-S14.
- [15] Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon JL, Nieminen MS, Piérard L, Remme WJ and Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. [Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26: 1115-1140.
- [16] Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, Storrow AB, Christenson RH and NACB Committee. National Academy of Clinical Biochemistry Laboratory Medicine practice guidelines: clinical utilization of cardi-

Diagnosis of dyspnea among elderly

- ac biomarker testing in heart failure. *Clin Biochem* 2008; 41: 210-221.
- [17] Mueller T, Gegenhuber A, Poelz W and Haltmayer M. Diagnostic accuracy of B type natriuretic peptide amino terminal proBNP in the emergency diagnosis of heart failure. *Heart* 2005; 91: 606-612.
- [18] Lainchbury JG, Troughton RW, Strangman KM, Frampton CM, Pilbrow A, Yandle TG, Hamid AK, Nicholls MG and Richards AM. N-terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: results from the BATTLESCARRED (NT-proBNP-Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) trial. *J Am Coll Cardiol* 2009; 55: 53-60.
- [19] Maisel AS, Koon J, Krishnaswamy P, Kazanegra R, Clopton P, Gardetto N, Morrisey R, Garcia A, Chiu A and De Maria A. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. *Am Heart J* 2001; 141: 367-374.