Diagnostic and Prognostic Utility of Brain Natriuretic Peptide in Subjects Admitted to the ICU With Hypoxic Respiratory Failure Due to Noncardiogenic and Cardiogenic Pulmonary Edema*

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Background: **Brain natriuretic peptide (BNP) is useful in diagnosing congestive heart failure (CHF) in patients presenting in the emergency department with acute dyspnea. We prospectively tested the utility of BNP for discriminating ARDS vs cardiogenic pulmonary edema (CPE).**

Methods: **We enrolled ICU patients with acute hypoxemic respiratory failure and bilateral pulmonary infiltrates who were undergoing right-heart catheterization (RHC) to aid in diagnosis. Patients with acute coronary syndrome, end-stage renal disease, recent coronary artery bypass graft surgery, or preexisting left ventricular ejection fraction ≤ 30% were excluded. BNP was measured at RHC. Two intensivists independently reviewed the records to determine the final diagnosis.**

Results: **Eighty patients were enrolled. Median BNP was 325 pg/mL (interquartile range [IQR], 82 to 767 pg/mL) in acute lung injury/ARDS patients, vs 1,260 pg/mL (IQR, 541 to 2,020 pg/mL) in CPE patients ($p = 0.0001$). The correlation between BNP and pulmonary capillary wedge pressure was modest ($r = 0.27$, $p = 0.02$). BNP offered good discriminatory performance for the final diagnosis (C-statistic, 0.80). At a cut point ≤ 200 pg/mL, BNP provided specificity of 91% for ARDS. At a cut point ≥ 1,200 pg/mL, BNP had a specificity of 92% for CPE. Higher levels of BNP were associated with a decreased odds for ARDS (odds ratio, 0.4 per log increase; $p = 0.007$) after adjustment for age, history of CHF, and right atrial pressure. BNP was associated with in-hospital mortality ($p = 0.03$) irrespective of the final diagnosis and independent of APACHE (acute physiology and chronic health evaluation) II score.**

Conclusion: **In ICU patients with hypoxemic respiratory failure, BNP appears useful in excluding CPE and identifying patients with a high probability of ARDS, and was associated with mortality in patients with both ARDS and CPE. Larger studies are necessary to validate these findings.**

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Key words: ARDS; brain natriuretic peptide; cardiogenic pulmonary edema; respiratory failure; Swan-Ganz catheter

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; BNP = brain natriuretic peptide; CHF = congestive heart failure; CPE = cardiogenic pulmonary edema; FIO_2 = fraction of inspired oxygen; GFR = glomerular filtration rate; IQR = interquartile range; LVEF = left ventricular ejection fraction; OR = odds ratio; PCWP = pulmonary capillary wedge pressure; RHC = right-heart catheterization; ROC = receiver operating characteristic

Acute hypoxic respiratory failure secondary to pulmonary edema is a common reason for admission to the ICU and is associated with substantial morbidity and mortality. The differential diagnosis is challenging in cases requiring distinction between cardiogenic pulmonary edema (CPE) and ARDS/acute lung injury (ALI).[1–5] The most widely used clinical definition of ARDS/ALI is based on the acute onset of hypoxemia, chest radiography, risk factors, and a pulmonary capillary wedge pressure (PCWP) < 18 mm Hg, or absence of clinical evidence of elevated left atrial filling pressures.[3] However, clinical estimation of PCWP is notoriously inaccurate,[6] and its measurement requires the performance of right-heart catheterization (RHC) using a Swan-Ganz catheter, which is invasive and costly,[7] and has been associated with neutral[8–10] or potentially adverse clinical outcomes.[11] Nonetheless, the distinction between CPE and ARDS is important clinically since the management and the prognosis of these conditions are different.[12] Therefore, a simple noninvasive test to assist with this distinction would be highly desirable.

Brain natriuretic peptide (BNP) secretion is markedly increased beyond the physiologic range by pathologic ventricular volume and pressure overload.[13,14] The blood concentration of BNP is significantly elevated in patients with heart failure[15,16] and is useful in the diagnostic evaluation of acute dyspnea.[17,18] While there are data regarding the correlation of BNP with PCWP,[19,20] and in the differential diagnosis of shock,[21] there are few data directly evaluating the clinical use of BNP in the diagnosis of ARDS vs CPE in the critically ill patient.[22] Therefore, we planned a prospective study to assess the utility of measuring BNP to assist in the diagnostic and prognostic evaluation of patients with hypoxemic respiratory failure due to suspected CPE or non-CPE.

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Materials and Methods

Study Population

Between March 26, 2004, and May 1, 2005, 80 patients with acute hypoxemic respiratory failure undergoing RHC on the basis of diagnostic uncertainty regarding the etiology of respiratory failure as judged necessary by the treating physicians were enrolled in one surgical and two medical ICUs in two university-affiliated, tertiary care hospitals. Patients undergoing RHC for other reasons, such as guiding hemodynamic support, were not eligible for participation. The research protocol was approved by the institutional review boards of the two hospitals, and written informed consent for participation was obtained from all subjects or legal surrogate.

Inclusion criteria were as follows: (1) admission to a medical or surgical/trauma ICU with acute onset of hypoxemic respiratory failure with a Pao_2/fraction of inspired oxygen (Fio_2) < 300; (2) bilateral pulmonary infiltrates on chest radiography; and (3) diagnostic uncertainty requiring insertion of a Swan-Ganz catheter. Key exclusion criteria were as follows: (1) acute coronary syndrome as the diagnosis for ICU admission; (2) acute or chronic renal failure on renal replacement therapy; (3) CABG within 2 weeks; (4) measurement of BNP in the present hospitalization prior to enrollment; and (5) known preexisting left ventricular ejection fraction (LVEF) $< 30\%$. An impaired LVEF first documented in the ICU was not a basis for exclusion. During the enrollment period, 234 ICU patients underwent RHC in the participating ICUs. All patients undergoing RHC who met eligibility criteria with study staff available were enrolled, including during night and weekend hours.

Study Procedures

On enrollment, prior to performance of the RHC, and without knowledge of the BNP results, a physician caring for the patient recorded the most likely diagnosis (CPE vs ARDS/ALI). On placement of the introducer for the Swan-Ganz catheter, an ethylenediamine tetra-acetic acid-anticoagulated whole-blood sample was obtained. All hemodynamic measurements were performed by one investigator (D.K.) using a standard technique. Three measurements were performed at end-expiration, and the results were averaged. BNP was measured immediately after sample acquisition with a well-validated immunoassay (Triage; Biosite; San Diego, CA)[18] by laboratory personnel blinded to the clinical status of the patient. BNP results were blinded until after locking the clinical database and were not known by managing physicians or study staff. Echocardiography was not required by the protocol, but data were captured whenever available ($n = 74$, 91%).

Determination of Final Diagnosis

Two experienced attending intensivists (A.M. and D.T.) blinded to BNP results independently reviewed all patient records at least 10 days after enrollment. Using all other available diagnostic information that were collected during routine clinical care, they categorized an adjudicated final diagnosis as ARDS, CPE, mixed edema, or neither. The expert reviewers used the American-European consensus conference definition for the