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

diagnosis of ARDS/ALI[3] integrating all available data at the time of RHC as well as from follow-up, such as the clinical course and effect of positive pressure ventilation on hemodynamic measurements[23,24] There was initial agreement between the two experts in 76 of 80 cases. In case of disagreement, the two experts reviewed the disputed cases together and reached a consensus.

Statistical Analysis

Categorical data are reported as proportions, and continuous data are reported as medians. Analyses of categorical variables were performed using the Fisher exact test. Analyses of continuous variables were performed using nonparametric tests or using log-transformed data. Because BNP was skewed, log-transformed BNP was used in correlation and regression analyses. Receiver operating characteristic (ROC) curve analyses were graphically represented. For each cut point of BNP, sensitivity, specificity, and positive and negative predictive values were reported.

In order to assess for an independent association between BNP and the final diagnosis, a multivariable logistic regression model was constructed with the diagnosis of ARDS as the dependent variable and log BNP, age, gender, body mass index, use of pressors, history of congestive heart failure (CHF), estimated glomerular filtration rate (GFR) [modified diet in renal disease equation], and mean right atrial and pulmonary artery systolic pressures as the independent covariates. Due to the limited sample size, a parsimonious $p < 0.05$ was required for entry into the model, with $p < 0.1$ for retention. After nonsignificant covariates were eliminated, the final model was refitted to minimize the effect of missing data. The discriminatory capacity of the model was assessed using ROC curve estimation, and goodness of fit was assessed by the Hosmer-Lemeshow test. In further exploratory analyses, the utility of BNP as a covariate was compared to that of PCWP. We additionally tested whether the inclusion of echocardiographic parameters (LVEF, wall-motion abnormality) as potential covariates impacted the association between BNP and diagnosis.

Finally, a multivariable logistic regression model was constructed to evaluate the association of log-BNP with in-hospital mortality after adjusting for the APACHE (acute physiology and chronic health evaluation) II score and other covariates associated with mortality with $p < 0.05$ (gender, GFR, history of CHF, use of pressors, right ventricular dysfunction or hypokinesis, serum bicarbonate concentration, and international normalized ratio). In this model, covariates already included in the APACHE II score (*eg*, age, BP parameters, temperature) were not included separately in the model to avoid colinearity. All analyses were performed using statistical software (Stata Version 8.2; StataCorp; College Station, TX).

Results

Baseline characteristics of the 80 enrolled patients are presented in Table 1 stratified according to the final expert diagnosis. Medical and surgical ICUs

Table 1—*Baseline Characteristics at Enrollment by Expert Diagnosis

Characteristics	ALI/ARDS (n = 51)	CPE (n = 23)	Mixed (n = 6)	p Value for ALI/ARDS vs CPE
Demographics				
Age, yr	62 (52–73)	70 (60–85)	64.5 (51–74)	0.046
Male gender	62.8	39.1	66.7	0.078
White race	88	86.4	100	1.0
History of cardiac disease				
CHF	16	52.2	33.3	0.004
Myocardial infarction	16	13	16.7	1.0
Angina	8	9	20	1.0
Prior percutaneous coronary intervention	12	17.4	16.7	0.72
Prior coronary artery bypass graft surgery	9.8	21.7	16.7	0.27
History of diabetes	19.6	39.1	33.3	0.091
History of pulmonary disease				
COPD	16	13	33.3	1.0
Asthma	10	8.7	0	1.0
Pulmonary hypertension	9.8	8.7	0	1.0
Restrictive lung disease	6	8.7	0	0.65
ICU presentation				
Medical ICU	53	69.6	66.7	0.21
Surgical/trauma ICU	47.1	30.43	33.33	0.21
Intubation	78	78	50	1.0
Pressors/inotropes	52	39	67	0.33
APACHE II score	20 (15.5–25)	20 (14–28)	17 (14–28)	0.82
Systolic BP, mm Hg	107 (93–125)	112 (97–148)	92.5 (78–102)	0.46
Heart rate, beats/min	98 (88–114)	88 (79–116)	80.5 (75–88)	0.16
Temperature, °F	100.2 (99–101.5)	99.6 (99.2–100.5)	100.9 (100.6–101.9)	0.34
WBC count, ×1,000/μL	14.1 (9.2–17.2)	10.8 (9–15.6)	11.1 (2.8–11.1)	0.38
Lactate, mmol/L	2.1 (1.3–3.4)	1.9 (1.3–4.2)	1.8 (1.5–2.1)	0.82
Estimated GFR, mL/min	67 (48–92)	35 (18–63)	68 (33–75)	0.009
Positive culture results	43.1	47.8	66.7	0.80

*Data are presented as median (IQR) or %.

were equally represented (58% and 42% of the patients, respectively). Patients were high risk based on the APACHE II score and other clinical criteria. Subjects with CPE were more likely to be older, to have a history of CHF, and to have worse kidney function. There was no statistical difference in the frequency of prior cardiac disease, and the overall severity of illness was indistinguishable as captured by the APACHE II score. In addition, there were no significant differences in temperature, systolic BP, heart rate, WBC count, lactate levels, proportion of patients with documented bacteremia, or proportion of patients receiving one or multiple pressors between the ALI/ARDS and CPE groups. The most frequent ICU admitting diagnoses were sepsis (34%) and pneumonia (15%), followed by respiratory failure (12%), abdominal surgery (9%), CHF (8%), pancreatitis (6%), and ischemic bowel (5%).

Subjects were enrolled at a median of 3 days (25 to 75% interquartile range [IQR], 1 to 9 days) following admission to the hospital, and at a median of 0 days (IQR, 0 to 2 days) from the time of admission to the ICU. The median fluid input/output from the time of admission to the ICU until the performance of RHC was + 4,100 mL (IQR, 1,000 to 9,250 mL). The median concentrations of BNP and echocardiographic, radiographic, ventilatory, and hemodynamic data are presented in Table 2. The radiographic and ventilatory data presented were collected at the time of hemodynamic measurements. Echocardiographic data collected and presented were the most recent data in relation to the hemodynamic assessment, of which 54% were within 48 h between the two studies. Subjects with a diagnosis of ARDS had a higher median ejection fraction ($p = 0.03$) and lower mean right atrial ($p = 0.0006$) and end-expiratory wedge pressures ($p = 0.001$) compared to subjects with CPE, and were more likely to be managed with higher levels of positive end-expiratory pressure ($p = 0.004$).

BNP and Diagnosis of ARDS

The initial clinical diagnosis of CPE by the treating physician prior to RHC was in agreement with the experts' final diagnosis in only 48.6%, with the remainder classified as ARDS by expert final diagnosis (Fig. 1). In contrast, the initial diagnosis of ARDS by the clinician was more frequently in agreement with the experts' final diagnosis (Fig 1). Patients with a diagnosis of ARDS had significantly lower median levels of BNP compared to subjects with a diagnosis of CPE (325 pg/mL vs 1,260 pg/mL, $p = 0.0001$) [Table 2]. This observation remained consistent when restricted to those for whom the initial clinical diagnosis was CPE (388 pg/mL vs 1,280 pg/mL, $p = 0.01$). In addition, BNP was modestly correlated with end-expiratory PCWP

Table 2—*Radiologic, Echocardiographic, Hemodynamic, and BNP Data

Variables	ALI/ARDS (n = 51)	CPE (n = 23)	Mixed (n = 6)	p Value for ALI/ARDS vs CPE
Chest radiography				
Infiltrates on two quadrants	44.9	43.4	83.3	0.77
Infiltrates on four quadrants	22.4	30.43	16.7	0.77
Pleural effusions	59.2	65.2	50	0.80
Cardiomegaly	30	43.5	83.3	0.30
Echocardiography				
LVEF, %	56.5 (50–65)	52.5 (35–55)	35 (20–35)	0.031
Left ventricular dilatation	2.3	4.8	40	0.55
Mitral regurgitation ≥ grade 2	9.3	22.73	20	0.25
Right ventricular dilatation/hypokinesis	31.8	30	60	1.0
Wall-motion abnormalities	11.6	36.3	80	0.025
Ventilatory data				
Po_2/Fio_2	163 (96–240)	166.3 (70.3–260)	190.8 (55.6–224)	0.26
Tidal volume, mL/kg	5.8 (5.2–6.8)	6.3 (5–7.7)	7.7 (6–9.4)	0.36
Positive end-expiratory pressure, cm H_2O	10 (5–15)	5 (5–8)	5 (5–7)	0.0022
Fio_2, %	0.7 (0.5–1)	0.6 (0.45–0.8)	0.5 (0.5–0.6)	0.15
Po_2, mm Hg	95 (76–126)	98 (90–122)	94.5 (76–115)	0.46
Hemodynamics				
Right atrial mean pressure, mm Hg	12 (10–15)	17.5 (14–20)	16.5 (15–20)	0.0006
Pulmonary artery systolic pressure, mm Hg	41 (36–50)	58 (50–62)	51.5 (41–60)	0.0001
End-expiratory wedge pressure, mm Hg	16 (13–18)	20 (16–25)	22 (18–25)	0.001
Cardiac index, L/min/m^2	3.18 (2.71–4.1)	3.09 (2–4.4)	2.08 (1.9–4.43)	0.56
BNP, pg/mL	325 (82–767)	1,260 (541–2,020)	837.5 (558–1,300)	0.0001

*Data are presented as % or median (IQR).

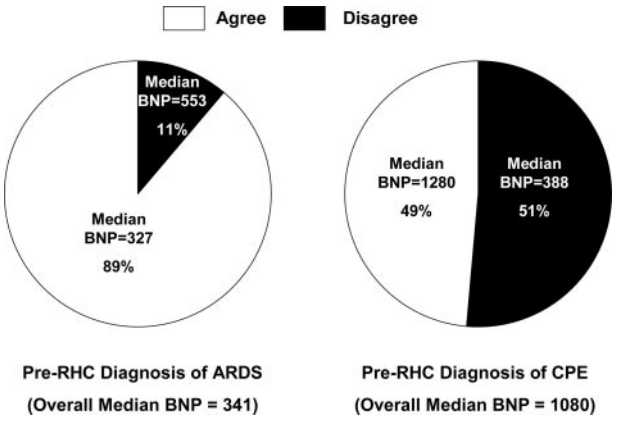

FIGURE 1. Concordance of clinician pre-RHC diagnosis with expert diagnosis (including RHC data).

($r = 0.27$, $p = 0.02$). Of note, when PCWP was used alone to categorize patients as ALI/ARDS vs CPE, patients categorized with ARDS (PCWP < 18 mm Hg) similarly had significantly lower median levels of BNP compared to those with PCWP ≥ 18 mm Hg (550 pg/mL vs 1,192 pg/mL, $p = 0.0003$).

The area under the ROC curve for BNP in relation to the expert's final diagnosis of ARDS was 0.80. Including patients with a mixed diagnosis as CPE had minimal impact on the area under the ROC curve (C-statistic, 0.79). The diagnostic performance of BNP at several cut points is presented in Tables 3, 4. At a cut point ≤ 200 pg/mL, BNP provided a specificity of 91% and a positive predictive value of 91% for the diagnosis of ARDS. At a cut off point ≥ 1.200 pg/mL, BNP had a specificity of 92% and a positive predictive value of 75% for the diagnosis of CPE. The use of the lower cut-off point ≤ 200 pg/mL for BNP measurement would have reclassified 8 of 36 patients (22%) with a pre-RHC assessment of CPE as ARDS. The use of the higher cut-off point $\geq 1,200$ pg/mL would have reclassified 1 of 35 subjects (3%) with a pre-RHC assessment of ARDS instead as CPE. Including patients with a mixed diagnosis as CPE had minimal impact on the diagnostic performance of BNP (Tables 3, 4). Moreover, use of the PCWP alone to categorize patients with ARDS vs CPE did not qualitatively alter the results (C-statistic, 0.75; specificity, 93% for ARDS using BNP ≤ 200 pg/mL; specificity, 87% for CPE using BNP $\geq 1,200$ pg/mL).

In multivariable analyses, a higher concentration of BNP was associated with a decreased odds of the diagnosis of ARDS (odds ratio [OR], 0.4 per log increase in BNP; $p = 0.027$) after adjustment for baseline covariates. The final covariates in the model included log BNP, right atrial mean pressure, and a history of CHF. The overall C-statistic for the model was 0.88, with adequate fit as assessed by the Hosmer-Lemeshow test ($p > 0.3$). In these analyses, indexes of renal function (both BUN as well as GFR) or the pulmonary artery systolic pressure were not associated with the diagnosis of ARDS.

In exploratory analyses, log BNP was as discriminatory a covariate as PCWP (C-statistic of model substituting PWCP for BNP, 0.88) and provided additional explanatory power to that of PCWP alone ($p = 0.017$ by likelihood ratio test). Further sensitivity analyses including adjustment for echocardiographic parameters (LVEF and presence of a wall-motion abnormality) in patients in whom these data were available resulted in only a modest shift in the estimate of the association between BNP and ARDS (adjusted OR, 0.5 [confidence interval, 0.2 to 1.0] per log increase in BNP).

BNP and In-hospital Mortality

BNP showed a strong graded relationship with mortality risk in subjects with ARDS and CPE ($p = 0.03$; Fig 2). This association remained independent after considering APACHE II score and other covariates associated with mortality in univariate analyses. Only two parameters remained in the

Table 3—*Performance Characteristics of Various Cut Points of BNP Excluding Patients With a "Mixed" Diagnosis**

Cut Points	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
For ARDS						
< 100 (n = 13, 18%)	100 (75–100)	38 (26–52)	26 (15–40)	100 (85–100)		0.74
< 200 (n = 22, 30%)	91 (71–99)	41 (28–56)	40 (26–55)	91 (72–99)	4.60	0.66
< 400 (n = 33, 45%)	88 (72–97)	48 (32–64)	58 (43–72)	83 (61,95)	3.34	0.51
For CPE						
$\geq 1,000$ (n = 21, 29%)	62 (38–82)	81 (67–90)	57 (34–77)	84 (71–93)	3.53	0.52
$\geq 1,200$ (n = 16, 22%)	75 (48–93)	81 (68–90)	52 (31–73)	92 (81–98)	6.52	0.52
$\geq 2,000$ (n = 8, 11%)	75 (35–97)	74 (61–84)	26 (10–48)	96 (86–100)	6.52	0.77

*Data are presented as % (95% confidence interval) unless otherwise indicated.

Table 4—*Performance Characteristics of Various Cut Points of BNP Including Mixed Diagnosis Patients as CPE

Cut Points	Positive Predictive Value	Negative Predictive Value	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
For ARDS						
< 100 (n = 13, 16%)	100 (75–100)	44 (32–57)	26 (15–40)	100 (88–100)		0.74
< 200 (n = 22, 28%)	91 (71–99)	47 (34–61)	40 (26–55)	93 (77–99.9)	5.8	0.64
< 400 (n = 34, 43%)	85 (69–95)	53 (38–68)	58 (43–72)	83 (64–94)	3.36	0.51
For CPE						
≥ 1,000 (n = 23)	65 (43–84)	75 (62–86)	52 (33–71)	84 (71–93)	3.23	0.58
≥ 1,200 (n = 18)	78 (52–94)	75 (63–86)	48 (29–67)	92 (81–98)	6.03	0.56
≥ 2,000 (n = 19)	78 (40–97)	69 (56–79)	24 (10–44)	96 (86–99.9)	6.03	0.79

*Data are presented as % (95% confidence interval) unless otherwise indicated.

final model as independently associated with mortality: BNP (OR, 1.6 for each log increase; $p = 0.03$) and the APACHE II score (OR, 1.1 for each point increase; $p = 0.002$), with an overall C-statistic of the model of 0.76 and adequate goodness of fit ($p > 0.6$). Of note, the independent association between BNP and mortality remained after further adjustment for PCWP.

Discussion

Our findings demonstrate the potential of testing for BNP to add to the clinical history, physical examination, and routine diagnostic data to exclude CPE in patients with respiratory failure in the ICU. We found that a low concentration of BNP (< 200 pg/mL) provided a very high specificity for the diagnosis of ARDS, independent of traditional clinical variables. Importantly, a low level of BNP would have reliably excluded CPE in 8 of 18 patients (44%) for whom the initial clinical impression was that the cause was cardiogenic and the final experts' diagnosis was ARDS. Notably, the concentration of BNP was independently associated with mortality in critically ill patients, regardless of the etiology of the hypoxemic respiratory failure.

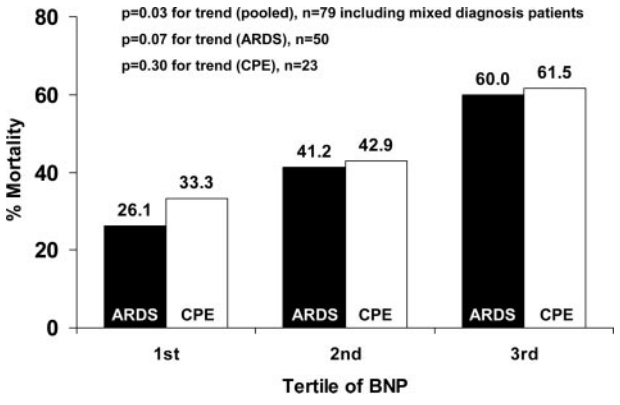

Figure 2. In-hospital mortality stratified by BNP.

Potential Diagnostic Applications

The clinical diagnosis of ALI/ARDS is challenging, and available diagnostic criteria are far from ideal.[1] Even the performance of open-lung biopsy has limitations.[25] Accurate determination and interpretation of the hemodynamic data in a real-world ICU is also difficult.[26–32]

Our data indicate that a strategy that employs BNP as an initial diagnostic test is likely to be useful in conjunction with standard clinical tools. In patients with a BNP level that is very low (*eg*, < 200 pg/mL) the probability of ARDS is very high and false-positive test results are few (< 10%); thus, invasive testing might be deferred. In patients with very high BNP levels, the probability of CPE is substantially increased and similarly the additive value of hemodynamic monitoring less certain. For those with intermediate concentrations of BNP (from 200 to 1,200 pg/mL, 49% of our population), the result does not substantially alter the posttest probability, and thus additional diagnostic evaluation should be performed if there is diagnostic uncertainty. While the value of a pulmonary artery catheter is somewhat controversial, it remains among the additional diagnostic alternatives that may be considered.[33] This proposed strategy (Fig 3) reflects our observation that the potential for BNP to add to present tools is greatest when framed for its negative predictive value for CPE, and the opportunity to avoid invasive and more costly evaluation through use of a noninvasive and relatively inexpensive test. Our study reinforces that while statistically significant, the correlation between BNP and PCWP is poor,[19–21] and thus a single BNP measurement is a

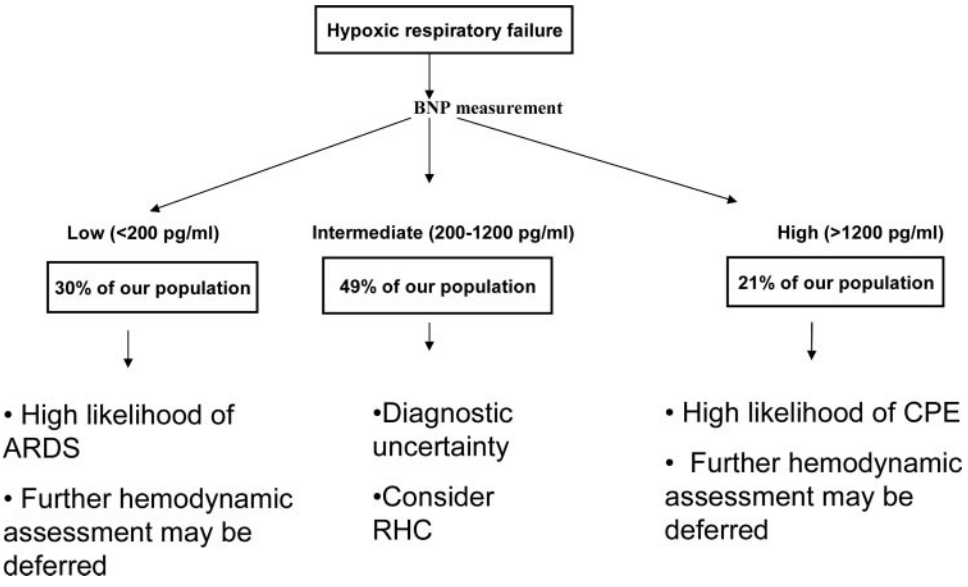

FIGURE 3. Possible algorithm for clinical application of BNP testing in patients with hypoxemic respiratory failure of uncertain etiology.

suboptimal substitute for measurement of filling pressures if quantitative rather than qualitative data are required.

Prognostic Implications

The observation that BNP can be elevated in patients with ARDS (with levels often >100 pg/mL, which is considered the threshold for diagnosis of CHF in patients with dyspnea) is consistent with previous studies[34–37] showing that BNP levels may be significantly increased in the ICU patients in relation to factors beyond pressure and volume overload. Importantly, we found that the association between BNP and outcome was independent of a comprehensive array of other traditional clinical tools.

Limitations

The strengths of this study include the mandatory assessment of the physician's pre-RHC diagnoses, the use of expert diagnosis as the "gold standard," and the thorough characterization of other clinical, hemodynamic, and diagnostic data. The following limitations should be recognized. We enrolled only patients with hypoxic respiratory failure undergoing RHC for diagnostic purposes as judged indicated by the treating physicians. Thus, by design, the study enrolled a high-risk cohort of patients in whom the diagnosis was particularly challenging and/or critical. The high mortality rate observed in our study is congruent with this aspect. In addition, we excluded patients with known preexisting severe systolic dysfunction since BNP may remain elevated even after the filling pressures are normalized,[15] and those with acute coronary syndromes[13,38] and with renal failure since both conditions may lead to increased BNP concentration. Although the principles are reasonably expected to apply generally to similar ICU populations, including less complex patients with hypoxemic respiratory failure, the cut points suggested by our analyses were determined by ROC curve analysis in this data set and warrant validation. In addition, the absence of a single objective "gold standard" for diagnosis of ARDS is a challenge inherent to all studies of diagnostic testing for this syndrome. We took a rigorous approach of independent expert review, blinded to BNP data, using established criteria. Nevertheless, it is important to recognize that ARDS is a clinical syndrome, and its diagnosis requires the consideration of multiple clinical, radiographic, laboratory, and hemodynamic data along with clinical judgment. Lastly, while the number of patients enrolled in our study ($n = 80$) is larger than in prior studies[19–22] addressing the use of BNP in this syndrome ($n = 40$ to 50), our study is still small. In light of this and the other limitations we have highlighted, prospective validation in larger studies is needed before integrating this strategy into clinical practice.

CONCLUSION

Measurement of BNP in conjunction with other clinical and laboratory assessments may be useful in the diagnostic and prognostic evaluation of patients admit-

ted to the ICU with hypoxemic respiratory failure. In particular, BNP may be most useful for excluding CPE in this setting. If validated in future prospective studies, measurement of natriuretic peptides may obviate the need for an invasive procedure in some cases.

References

1 Ware L, Matthay M. The acute respiratory distress syndrome. N Engl J Med 2000; 342:1334–1349
2 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–1308
3 Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824
4 Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury: predictors of mortality. Am J Respir Crit Care Med 1995; 152:1818–1824
5 Sloane PJ, Gee MH, Gottlieb JE, et al. A multicenter registry of patients with acute respiratory distress syndrome: physiology and outcome. Am Rev Respir Dis 1992; 146:419–426
6 Eisenberg PR, Jaffe AS, Schuster DP. Clinical evaluation compared to pulmonary artery catheterization in the hemodynamic assessment of critically ill patients. Crit Care Med 1984; 12:549–553
7 Mermel LA, Maki DG. Infectious complications of Swan-Ganz pulmonary artery catheters: pathogenesis, epidemiology, prevention, and management. Am J Respir Crit Care Med 1994; 149:1020–1036
8 Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003; 348:5–14
9 Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 2005; 366:472–477
10 Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 2006; 354:2213–2224
11 Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients: SUPPORT Investigators. JAMA 1996; 276:889–897
12 Brower RG, Ware LB, Berthiaume Y, et al. Treatment of ARDS. Chest 2001; 120:1347–1367
13 de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362:316–322
14 Sudoh T, Kangawa K, Minamino N, et al. A new natriuretic peptide in porcine brain. Nature 1988; 332:78–81
15 Kazanegra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001; 7:21–29
16 Maeda K, Tsutamoto T, Wada A, et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135:825–832
17 Davis M, Espiner E, Richards G, et al. Plasma brain natriuretic peptide in assessment of acute dyspnoea. Lancet 1994; 343:440–444
18 Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347:161–167
19 Dokainish H, Zoghbi WA, Lakkis NM, et al. Optimal noninvasive assessment of left ventricular filling pressures: a comparison of tissue Doppler echocardiography and B-type natriuretic peptide in patients with pulmonary artery catheters. Circulation 2004; 109:2432–2439
20 Forfia P, Watkins S, Rame J, et al. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. J Am Coll Cardiol 2005; 45:1667–1671
21 Tung RH, Garcia C, Morss AM, et al. Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. Crit Care Med 2004; 32:1643–1647
22 Jefic D, Lee JW, Savoy-Moore RT, et al. Utility of B-type natriuretic peptide and N-terminal pro B-type natriuretic peptide in evaluation of respiratory failure in critically ill patients. Chest 2005; 128:288–295
23 Jardin F, Genevray B, Brun-Ney D, et al. Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. Chest 1985; 88:653–658
24 Pinsky M, Vincent JL, De Smet JM. Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. Am Rev Respir Dis 1991; 143:25–31
25 Patel SR, Karmpaliotis D, Ayas NT, et al. The role of open-lung biopsy in ARDS. Chest 2004; 125:197–202
26 Putterman C. The Swan-Ganz catheter: a decade of hemodynamic monitoring. J Crit Care 1989; 4:127–146
27 Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. Am Rev Respir Dis 1982; 126:166–170
28 Morris AH, Chapman RH, Gardner RM. Frequency of technical problems encountered in the measurement of pulmonary artery wedge pressure. Crit Care Med 1984; 12:164–170
29 O'Quin R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology, measurement, and interpretation. Am Rev Respir Dis 1983; 128:319–326
30 Lessard MR, Lofaso F, Brochard L. Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. Am J Respir Crit Care Med 1995; 151:562–569
31 Gorini M, Misuri G, Duranti R, et al. Abdominal muscle recruitment and PEEPi during bronchoconstriction in chronic obstructive pulmonary disease. Thorax 1997; 52:355–361
32 Sibbald WJ, Driedger AA, Myers ML, et al. Biventricular function in the adult respiratory distress syndrome. Chest 1983; 84:126–134
33 Pulmonary Artery Catheter Consensus Conference: consensus statement. Crit Care Med 1997; 25:910–925
34 McLean AS, Huang SJ, Nalos M, et al. The confounding effects of age, gender, serum creatinine, and electrolyte concentrations on plasma B-type natriuretic peptide concentrations in critically ill patients. Crit Care Med 2003; 31:2611–2618
35 Wiese S, Breyer T, Dragu A, et al. Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium: influence of angiotensin II and diastolic fiber length. Circulation 2000; 102:3074–3079
36 Silva JA, Chan AW, White CJ, et al. Elevated brain natriuretic peptide predicts blood pressure response after stent revascularization in patients with renal artery stenosis. Circulation 2005; 111:328–333
37 Brueckmann M, Huhle G, Lang S, et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. Circulation 2005; 112:527–534
38 Omland T, Aakvaag A, Bonarjee VV, et al. Plasma brain natriuretic peptide as an indicator of left ventricular systolic function and long-term survival after acute myocardial infarction: comparison with plasma atrial natriuretic peptide and N-terminal proatrial natriuretic peptide. Circulation 1996; 93:1963–1969