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Prognostic value of plasma N-terminal probrain natriuretic peptide levels in the acute respiratory distress syndrome

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Abstract

Objective—Patients with acute respiratory distress syndrome suffer from profound cardiac and pulmonary derangement, including right ventricular strain and noncardiogenic pulmonary edema, which may potentially alter concentrations of cardiac natriuretic peptides. We sought to determine whether N-terminal probrain natriuretic peptide (NT-proBNP) levels are elevated in acute respiratory distress syndrome and whether they can serve as a marker of prognosis in this setting.

Design—Prospective study.

Setting—Tertiary-care academic medical center.

Patients—One hundred seventy-seven acute respiratory distress syndrome subjects enrolled in a prospective intensive care unit cohort.

Interventions—None.

Measurements and Main Results—NT-proBNP was measured from blood taken within 48 hrs of acute respiratory distress syndrome onset. Patients were followed for the primary outcome of 60-day mortality and secondary outcomes of organ dysfunction and ventilator-free days. Seventy patients died (40%). Median NT-proBNP level was 3181 ng/L (interquartile range 723–9246 ng/L). NT-proBNP levels were significantly higher among nonsurvivors ($p < .0001$). Receiver operating curve analysis revealed an optimal NT-proBNP cut-point of 6813 ng/L for predicting death. Patients with levels above the cut-point had significantly higher odds of mortality on multivariable analysis (odds ratio 2.36, 95% confidence interval 1.11–4.99, $p = .02$) than those with levels below the cut-point. Kaplan-Meier survival analysis showed that this difference emerged early and was sustained ($p < .0001$). Patients with elevated NT-proBNP also had higher organ dysfunction scores ($p < .0001$) and fewer ventilator free days ($p = .03$) than those with lower NT-proBNP levels.

Conclusions—NT-proBNP levels are elevated among acute respiratory distress syndrome patients and parallel the severity of the syndrome and likelihood for morbidity and mortality. This demonstrates the potential utility of this biomarker for prognosis in this disease.

Keywords

acute respiratory distress syndrome; prognosis; biological markers; N-terminal pro-BNP

The pathophysiology of the acute respiratory distress syndrome (ARDS) is complex and may involve derangement of several facets of the cardiopulmonary system. The syndrome is characterized by uncontrolled systemic inflammation, endothelial injury, and profound capillary leak, resulting in alveolar filling and respiratory failure. Hypoxemia can result in pulmonary vasoconstriction, decreased myocardial oxygen delivery, and a compensatory increase in cardiac output, all of which can contribute to myocardial strain. As the disease progresses, lung fibrosis and pulmonary capillary obliteration can occur, further exacerbating this condition (1). In addition, mechanical ventilation may raise intrathoracic pressures sufficiently to affect myocardial function (2). Myocardial dysfunction in the setting of sepsis may also be associated with worse outcomes (3). Because ARDS and sepsis share many similar features, the same deleterious relationship with myocardial dysfunction is likely to be present in patients with ARDS.

There has been great interest in defining markers of prognosis or pathophysiology in ARDS. Because the syndrome is so heterogeneous in etiology and progression, clinical evaluation alone may not provide sufficient information to guide therapy (4). Although a number of serum proteins have been found to be diagnostically and prognostically relevant in patients with ARDS, these markers are not routinely available to clinicians (5–9). Thus, their utility in patient care is limited.

Natriuretic peptide assays, which include tests for levels of B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone N-terminal probrain natriuretic peptide (NT-proBNP), are widely available for use by clinicians. These cardiac markers have proven utility for diagnosis and/or prognostication in a variety of clinical settings, including myocardial infarction, shock, and pulmonary embolism (10–13). Given the evidence that extrapulmonary complications and cardiopulmonary strain play a major role in ARDS, it is likely that natriuretic peptide levels would be correspondingly elevated. Previous reports have shown conflicting results in regard to whether elevated BNP and NT-proBNP levels might be useful in predicting mortality among patients with respiratory failure (14, 15). Also, a prior report suggested that BNP levels could be useful in distinguishing acute lung injury from cardiogenic pulmonary edema (16). Eison et al. (17) previously studied the utility of atrial natriuretic factor in a small series of patients with ARDS and found that atrial natriuretic factor levels were elevated in patients with ARDS and that elevated levels were significantly correlated with pulmonary artery systolic pressure. Therefore, we sought to evaluate the characteristics of NT-proBNP levels in patients with ARDS, and to examine the potential diagnostic and prognostic value of this marker in the clinical setting.

METHODS

Study Design and Enrollment

Study patients were drawn from a prospective cohort assembled for a molecular epidemiology study of ARDS as previously described (18). Admissions to the intensive care units at the Massachusetts General Hospital (Boston, MA) from September 1999 to May 2005 were screened for ARDS risk factors, including sepsis, septic shock, pneumonia, trauma, multiple transfusions, or aspiration as previously defined (18). Exclusion criteria included age <18 yrs, presence of a comfort care directive, presence of diffuse alveolar hemorrhage, or chronic lung disease that would confound the diagnosis of ARDS, or immunosuppression due to medication or disease. Patients with neutropenia attributed to

sepsis or those treated with corticosteroids were not excluded. Informed written consent was obtained from subjects or surrogates. Patients were defined as having ARDS if they developed respiratory failure requiring intubation and met American-European Consensus Committee criteria for ARDS (19). In accordance with these criteria, patients with clinical evidence of heart failure or pulmonary arterial occlusion pressure (PAOP) >18 mm Hg were excluded. The decision to measure PAOP was left to treating clinicians. If PAOP was not measured, the presence of heart failure was determined by critical-care trained physicians who were directly involved with patient care. The Massachusetts General Hospital Human Subjects Committee approved the study.

Data Collection

Baseline demographic data were collected, including age, sex, and data used for calculation of an Acute Physiology and Chronic Health Evaluation (APACHE) III score. Patients were followed for the primary end point of 60-day mortality and the secondary end points of ventilator-free days and daily multiple organ dysfunction scores (MODS). Daily MODS on each intensive care unit day were recorded as defined according to Brussels criteria, with one point awarded for each organ system failure (20). Ventilator-free days were defined as the number of days between weaning from mechanical ventilation and death or discharge from the intensive care unit.

Sample Collection and Testing

Blood samples were taken from ARDS patients within 48 hrs of fulfillment of all ARDS criteria. Patients from whom samples could not be obtained within this time period were excluded. When these patients were compared with included patients, there were no significant differences in terms of age, APACHE III score, or other baseline characteristics. Samples were stored in ethylenediamine tetraacetic acid-treated plasma and frozen in storage at -80°C until testing. NT-proBNP levels were tested using a Roche Elecsys 2010 immunoassay analyzer according to manufacturer protocols. This assay has <0.001% cross-reactivity with BNP or other relevant neuropeptides, and has a detection limit of 5 ng/L with measuring range up to 35,000 ng/L; to achieve measurements greater than 35,000 ng/L, dilutions are necessary.

Comparison with Heart Failure Patients

NT-proBNP levels from patients with known heart failure were studied for comparison with patients in our study population. These patients were enrolled in the pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study, a prospective study of NT-proBNP levels in patients with dyspnea presenting to the emergency department at our institution. Criteria for study eligibility and heart failure diagnosis were previously described (11). NT-proBNP levels from those patients were tested using the same procedure in the same laboratory as the current study. A subgroup analysis of patients with and without pulmonary arterial catheters (PAC) was planned *a priori*. Patients were included in the PAC subgroup if they had a PAC in place at the time of blood sampling.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.1 (SAS Institute Incorporated, Cary, NC). Univariate analyses were performed using chi-squared tests, two-sample *t*-tests, or Wilcoxon's rank-sum tests as appropriate. A receiver operating curve (ROC) was constructed and "optimal" NT-proBNP cut-point for predicting mortality was determined using the Youden Index method (21). Patients were stratified into two groups according to whether their NT-proBNP level was above or below this cut-point. The association of NT-proBNP levels above the cut-point with mortality was tested after

adjustment for age and severity of illness (APACHE III) using these data as covariates in a logistic regression model. Other covariates of clinical relevance, including gender, presence of sepsis, septic shock, and renal failure were tested in the model using a stepwise selection algorithm and ultimately removed because no covariate met a criterion of $p \leq .02$ for inclusion or had a substantial impact on model fit. Sixty-day survival time data were also used to construct Kaplan-Meier curves according to cut-point strata. These curves were compared using log-rank testing. NT-proBNP levels were log-transformed to achieve normality and divided into log-quartiles. The effect of increasing NT-proBNP log-quartile on mortality rate was evaluated using the Cochrane-Armitage trend test. Repeated-measures analysis of variance was used to compare average daily MODS scores between strata. A generalized linear regression model was used to analyze the effect of sepsis and septic shock on elevation of NT-proBNP levels. p values of $\leq .05$ were considered statistically significant.

RESULTS

Study Population and NT-proBNP Levels

One hundred seventy-seven patients were included in the study. Baseline characteristics of the study population are displayed in Table 1, sorted by the primary outcome of survival at 60 days after onset of ARDS. Survivors were significantly younger than nonsurvivors and had significantly lower severity of illness as measured by APACHE III score, but otherwise did not differ in terms of the characteristics studied. The overall mortality rate was 40%. In descending order, the risk factors for ARDS were septic shock in 60% of patients, sepsis without shock in 30%, aspiration in 9%, multiple transfusions in 8% and trauma in 4% (i.e., some patients had more than one ARDS risk factor).

The median NT-proBNP concentration in the study population was 3181.0 ng/L with an interquartile range of 723–9246 ng/L. Levels for individual patients spanned virtually the entire range of the assay, with one patient having a near-undetectable concentration of 19 ng/L and two patients who had concentrations that exceeded the maximum measurable concentration of 70,000 ng/L.

Diagnostic Behavior of NT-proBNP in ARDS: Comparison with Patients with Heart Failure

Although the absence of clinically significant heart failure was required for the diagnosis of ARDS, only 64 patients from the study population (36%) had NT-proBNP levels that would have been considered to be within the normal range of the assay (0–1800 ng/L) for a population of patients presenting with acute dyspnea (11). In an effort to better understand the similarities and differences between NT-proBNP concentrations in ARDS and acute heart failure, we identified 60 patients (34%) who had a PAC placed in the present cohort (and therefore had confirmed PAOP < 18 mm Hg). Among these patients, only 16 (27%) had NT-proBNP levels below 1800 ng/L. Among the patients in whom heart failure was clinically excluded without invasive measurement, a higher proportion (48 of 117, 41%) of patients had NT-proBNP levels below 1800 ng/L. This difference in proportions achieved borderline statistical significance ($p = .06$).

NT-proBNP levels from the study population were compared with levels from patients with heart failure enrolled in the PRIDE study (Table 2). Among all ARDS patients, NT-proBNP levels were lower than those of patients with acute heart failure from the PRIDE study, although this difference was not statistically significant. However, the direction of the association varied according to the subgroup of ARDS patients. When the analysis was restricted to patients without PAC, the difference became significant, furthermore, those subjects with PAC actually had NT-proBNP levels that were significantly higher than those among PRIDE patients with acute heart failure.

Baseline characteristics of patients with and without PAC were compared to determine a basis for these variations (Table 3). Patients who had a PAC placed were significantly older and significantly more likely to have septic shock than other patients but were otherwise similar in terms of baseline characteristics.

The impact of sepsis and septic shock on NT-proBNP elevation was also evaluated. The majority of patients in this study had sepsis or septic shock as an inciting risk factor for ARDS (89%). Patients with sepsis had higher NT-proBNP levels (median 2131 $\pm$ interquartile range 464–5372 ng/L) than patients without sepsis (median 582 $\pm$ interquartile range 426–2032 ng/L) but this difference was not statistically significant. However, patients with septic shock had significantly higher NT-proBNP levels (median 5015 $\pm$ interquartile range 1217–13501 ng/L, $p = .001$). When entered into a generalized linear regression model, the presence of sepsis was significantly associated with increasing NT-proBNP ($p = .05$), however, when shock was added to the model this association lost significance and the presence of shock was highly associated with NT-proBNP elevation ($p = .004$).

NT-proBNP and ARDS Outcomes

When segregated by the primary outcome of 60-day mortality, ARDS nonsurvivors had significantly higher NT-proBNP levels than survivors (Fig. 1).

The results of the ROC analysis demonstrated an area under the curve of 0.66 with 95% confidence intervals of 0.57–0.74 ($p \leq .0001$); the optimal NT-proBNP cut-point for predicting mortality was 6813 ng/L, which had 80% sensitivity and 51% specificity. By comparison, generating a ROC using the APACHE III score alone to predict mortality showed a similar area under the curve of 0.72, 64% sensitivity, and 72% specificity.

When patients were grouped into strata according to NT-proBNP level above and below 6813 ng/L, the presence of NT-proBNP levels above the cut-point was significantly associated with increased odds of mortality, with an odds ratio of 4.24 (95% confidence intervals 2.17–8.27, $p = .0001$). This association remained significant even after adjusting for age and APACHE III score in the logistic regression model (Table 4). Kaplan-Meier curves constructed for these strata also showed significantly worse survival among patients in the higher NT-proBNP group (Fig. 2).

In an effort to better understand the relationship between NT-proBNP concentrations and outcomes—such as to examine whether the relationship between biomarker levels and mortality was a threshold or continuous risk—NT-proBNP results were log-transformed and divided into quartiles. In doing so, a monotonic increase in mortality associated with increasing NT-proBNP log-quartile was observed. This trend was statistically significant (Fig. 3).

Analyses were also conducted for the secondary outcomes of daily MODS and number of ventilator-free days. In concordance with the findings for the primary outcome of mortality, patients with NT-proBNP levels above the optimal ROC cut-point had significantly higher average daily MODS than other patients (Fig. 4). These patients also had significantly fewer ventilator free days (5.2 vs. 7.9, $p = .03$).

DISCUSSION

We determined that plasma NT-proBNP levels are commonly elevated in patients with ARDS, and that these levels are significantly higher in patients who died within 60 days of ARDS onset. The association of elevated plasma NT-proBNP levels with mortality in ARDS was robust and remained significant even after adjustment for confounders. This association

was also found to be relevant to survival time, and showed a significant monotonic trend in terms of increasing mortality rate with increasing log NT-proBNP level. Elevated NT-proBNP levels were also found to be associated with greater organ failure and fewer ventilator-free days, further demonstrating the robustness and relevance of these associations.

These findings support our hypothesis that cardiopulmonary strain associated with ARDS can result in elevation of NT-proBNP levels, and that these levels may provide useful information about pathophysiology and prognosis. Our results and the results of other reports point the way toward future research applications of the role of natriuretic peptide markers in patients with ARDS. Although the ability of NT-proBNP levels to independently predict mortality is modest, it is clear that the biomarker retains prognostic utility even after adjustment for severity of illness and should be considered an important part of the clinical and biochemical profile of patients with ARDS.

One unresolved issue is the source of natriuretic peptide elevation in patients with ARDS and/or septic shock. Although this has been suspected to be due to concomitant myocardial dysfunction, a recent large study of NT-proBNP levels in patients with septic shock found that NT-proBNP levels were poorly correlated with cardiac index (22). Right ventricular function may play a more important role in ARDS than in septic shock, however, the relationship between natriuretic peptide levels and right ventricular function has not been well studied. The role of fluid balance in these associations also remains unclear. The trend in management of sepsis and septic shock has been toward aggressive fluid resuscitation, including early goal-directed therapy in some cases (23). Conversely, the results of the recent Fluid and Catheter Therapy Trial study suggested that patients with ARDS may benefit from conservative fluid management later in the course of disease (24). It is conceivable that overly aggressive fluid management leads to increased myocardial strain with subclinical or clinically under-appreciated heart failure (reflected by NT-proBNP elevation). The fact that the presence of shock seems to be an important contributor to NT-proBNP elevation would seem to be in line with this hypothesis as well, as these patients would be expected to receive more aggressive fluid resuscitation than hemodynamically stable patients. Further study in this area should focus on more detailed measurements of cardiac function, particularly right ventricular function, in patients with ARDS to determine the causes of natriuretic peptide elevation. Patients should also be studied serially and with relation to fluid balance to determine whether differences in management play a role in altering these levels, and by the same token, whether these levels could be used to guide management.

We acknowledge that our study is limited by the fact that we were unable to study these variables. However, we believe that our results have helped define the directions that future research in this area might take. Among other limitations of our study, the ROC cut-point obtained from our data needs to be validated in other patient populations before definitive assertions can be made as to its validity. However, we would point out that the value is similar to a cut-point independently obtained from another large study population with critical illness (22). We were also limited by the characteristics of our patient population. Because most patients had ARDS related to sepsis and septic shock, we are unable to exclude the possibility that NT-proBNP level elevation occurred as a result of processes related to these underlying illnesses rather than to ARDS. We addressed this using a linear regression model, which indicated that the presence of sepsis was associated with increased NT-proBNP levels, but that this association was not significant when shock was added to the model. Further studies that include more subjects without sepsis would help further explore this relationship. We do not have data regarding the time course of elevation of NT-proBNP in ARDS, or the appropriate time point for sampling for prognostication; this is an important

point for future studies of this kind. Finally, the parent cohort for our study was established at a large tertiary-care academic center, and some patient populations (such as the immunosuppressed) were not included, both of which factors could limit the generalizability of these results somewhat.

With regard to the relationship between NT-proBNP levels and the presence of heart failure, while previous data have suggested that in some patient populations, natriuretic peptide levels above or below certain cut-points may provide reasonable diagnostic utility for distinguishing cardiogenic from noncardiogenic pulmonary edema (15), our results clearly are concordant with other studies showing that natriuretic peptides are less useful from a diagnostic perspective in the context of critical illness. Indeed, among the PAC subgroup analysis in our study, NT-proBNP levels appeared to separate in opposite directions according to the presence or absence of a PAC, with higher values seen in those with a documented PAOP <18 mm Hg. To some extent, this seems to be due to confounding by indication, with higher levels in the PAC group perhaps being driven by the more severely ill nature of the patients who received PAC placement (represented by older age and higher proportion of patients with septic shock), although interestingly, patients in both groups were similar in terms of other variables, including APACHE III score. Nonetheless, what these findings do appear to signify is that even among these patients, who by definition were confirmed to have PAOP <18 mm Hg in accordance with American-European Consensus Committee criteria for the diagnosis of ARDS, NT-proBNP levels may be significantly elevated to concentrations typically seen in patients with heart failure. In accordance with other data that suggest that natriuretic peptide levels show at best a mediocre correlation with PAOP (25), it seems that for clinical purposes NT-proBNP levels cannot definitively be used to identify an elevated PAOP. In interpreting these findings, it is important to note that while use of bedside PAC has been the gold standard for measurement of PAOP, there is potential for measurement error associated with use of this tool.

In summary, these data demonstrate that elevated NT-proBNP levels are associated with worse outcomes in patients with ARDS. This suggests the feasibility of using this assay as a prognostic marker in conjunction with other means of prognostic scoring and/or as part of a biochemical profile in such a patient population. In addition, the results suggest important new directions for further pursuit of such research. The causes of NT-proBNP elevation and whether these levels can be used to guide clinical management or shed further light on disease pathophysiology remain to be investigated.

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Figure 1. N-terminal probrain natriuretic peptide (*NT-proBNP*) levels stratified by 60-day mortality (bars represent 5%–95% percentile, *p* value stated for Wilcoxon's rank-sum test). *IQR*, interquartile range.

Figure 2. Survival time stratified by N-terminal probrain natriuretic peptide (*NT-proBNP*) concentration above or below the optimal cut-point of 6813 ng/L.

Figure 3. Relationship between N-terminal probrain natriuretic peptide (*NT-proBNP*) log quartiles and death (*p* value stated for chi-squared test of trend).

Figure 4.

Average daily multiple organ dysfunction scores (*MODS*) score stratified by N-terminal probrain natriuretic peptide (*NT-proBNP*) concentration above or below the optimal cut-point of 6813 ng/L. (p value stated for repeated-measures analysis of variance). *ARDS*, acute respiratory distress syndrome; *MODS*, multiple organ dysfunction score.

Table 1

Baseline characteristics of study population

	Survivors (n = 107)	Nonsurvivors (n = 70)	p
Female gender	50 (48%)	28 (40%)	NS
White race	97 (92%)	66 (94%)	NS
Age (mean $\pm$ SD)	54.7 ($\pm$ 18.3)	68.3 ($\pm$ 15.3)	<.0001
APACHE III score (mean $\pm$ SD)	73.2 ($\pm$ 23.5)	89.6 ($\pm$ 25.3)	<.0001
Septic shock	60 (56%)	46 (66%)	NS
Sepsis (without shock)	34 (32%)	19 (27%)	NS
Vasopressor treatment	69 (66%)	49 (72%)	NS
Creatinine > 2.0 mg/dL	22 (21%)	20 (29%)	NS
Diabetes history	24 (23%)	15 (21%)	NS
Smoking history	59 (67%)	40 (65%)	NS

APACHE, Acute Physiology and Chronic Health Evaluation; NS, nonsignificant.

Table 2

NT-proBNP levels from ARDS study population compared with PRIDE study heart failure patients

Category	NT-proBNP (median $\pm$ IQR) (ng/L)	<i>p</i> (vs. acute heart failure)
Acute heart failure (PRIDE, n = 209)	4054 (1689–9970)	Referent
All ARDS (n = 177)	3209 (842–10064)	NS
ARDS with PAC (n = 60)	5803 (1082–13723)	.05
ARDS without PAC (n = 117)	2506 (723–8602)	<.0001

NT-proBNP, N-terminal probrain natriuretic peptide; ARDS, acute respiratory distress syndrome; PAC, pulmonary arterial catheters; NS, nonsignificant; PRIDE, pro-BNP Investigation of Dyspnea in the Emergency Department; IQR, interquartile range.

Table 3

Baseline characteristics of patients with and without PAC

	With PAC (n = 60)	No PAC (n = 117)	<i>p</i>
Female gender	31 (52%)	48 (41%)	NS
White race	55 (92%)	110 (94%)	NS
Age (mean $\pm$ SD)	59.7 ($\pm$ 16.6)	54.7 ($\pm$ 18.8)	.04
APACHE III score (mean $\pm$ SD)	83.8 ($\pm$ 20.7)	77.6 ($\pm$ 22.7)	NS
Septic shock	43 (72%)	63 (54%)	.02
Sepsis (w/o shock)	13 (22%)	40 (34%)	NS
Vasopressor treatment	43 (74%)	77 (66%)	NS
Creatinine >2.0 mg/dL	13 (22%)	30 (26%)	NS
Diabetes history	17 (28%)	23 (20%)	NS
Smoking history	33 (67%)	66 (64%)	NS

PAC, pulmonary arterial catheters; NS, nonsignificant; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4

Logistic regression model for association of elevated NT-proBNP level with 60-day mortality

Variable	Odds Ratio	95% CI	<i>p</i>
NT-proBNP	2.36	1.11–4.99	.02
Age (per year)	1.05	1.02–1.07	<.0001
APACHE III (per point)	1.03	1.01–1.05	.006

NT-proBNP, N-terminal probrain natriuretic peptide; CI, confidential interval; APACHE, Acute Physiology and Chronic Health Evaluation.