Comparison of prognostic value of N-terminal pro-brain natriuretic peptide in septic and non-septic intensive care patients

Namik Ozcan, Ayse Ozcan, Cetin Kaymak, Hulya Basar, Mustafa Kotanoglu, Bektas Kose

Abstract

Introduction: The aim of this study is to compare the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in septic and non-septic intensive care patients.

Material and methods: Fifty consecutive patients admitted to the intensive care unit (ICU) were enrolled in either the septic or non-septic group according to the criteria in the International Sepsis Definitions Conference in 2001. Demographic and clinical data, procalcitonin and lactate levels at admission, and death within 28 days were registered. Five blood samples were collected from all patients for NT-proBNP measurements.

Results: Septic patients had higher APACHE II (19 (16.00–24.25) vs. 16 (13.00–18.25)), and SOFA (8 (5–10) vs. 6 (4–7)) scores ($p <0.05$). Procalcitonin levels were also higher in septic patients (3.33 (1.06–10.96) vs. 0.46 (0.26–1.01) ng/ml) and more patients required vasopressors in this group (9 (36%) vs. 2 (8%)) ($p < 0.05$). In the septic group, the correlation between mortality and the level of NT-proBNP was significant for each measurement, starting from the admission. In the non-septic group the correlation between mortality and the level of NT-proBNP was significant only at the 120th h.

Conclusions: We concluded that the level of NT-proBNP at admission is well correlated with 28-day mortality in septic ICU patients. However, single measurement of NT-proBNP levels in non-septic patients does not correlate with the 28-day mortality. Repeated measurements and an increasing trend of the NT-proBNP levels may show a correlation with mortality in non-septic intensive care patients.

Key words: NT-proBNP, intensive care unit, patient outcome assessment, critically ill.

Introduction

Brain natriuretic peptide (BNP) is a prohormone synthesized by the cardiac myocytes in response to pressure or volume overload. This peptide promotes diuresis, natriuresis, and vasodilation and inhibits the renin angiotensin system and the sympathetic nervous system. It is finally excreted by the kidneys. Utility of the BNP in diagnosis and guiding the treatment of heart diseases has been well documented in the literature [1–9].

Brain natriuretic peptide levels are found to be increased in septic patients in most studies. Increased levels of proinflammatory cytokines (IL1b, TNF-α, IL-6) stimulate secretion of BNP. These cytokines also con-
tribute to the development of septic myocardial depression [10].

Recently, a number of studies have reported the predictive value of BNP in the critically ill intensive care population. Although these studies had various designs and patient groups, most of them reported that BNP was an alternative predictor of outcome in the intensive care unit (ICU). The major emphasis in most of these studies was the correlation between elevated levels of BNP and the ICU outcome [11–17]. In contrast to other studies, Park et al. [18] suggested that instead of considering absolute levels, the trend of BNP might provide better prognostic utility in ICU patients.

The aim of this study was to compare the prognostic value of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels in septic and non-septic ICU patients.

Material and methods

Patient selection

This prospective observational study was performed in a 12-bed ICU of Ankara Research and Training Hospital. The study protocol was approved by the institutional review board. Written informed consent was obtained from the patients’ first degree relatives.

Fifty consecutive patients admitted to the ICU were enrolled either in septic (including sepsis, severe sepsis, and septic shock) or non-septic group (25 each) according to the criteria in the International Sepsis Definitions Conference of 2001. Exclusion criteria were age less than 18 years, evidence of any kind of current or previous heart disease, renal disease requiring renal replacement therapy, pregnancy, and acute cerebrovascular events. Patients who died before the fourth day of ICU admission were also excluded.

Study protocol

The same brand and model of ventilators (Galileo Gold, Hamilton Medical AG, Switzerland) were used for all patients who needed ventilatory support. Propofol and remifentanil infusions were used interchangeably for sedation as needed. All patients received low molecular weight heparin prophylaxis during the ICU stay. Vasopressor treatment included norepinephrine and dopamine infusions if needed.

Data collection

Demographic and clinical data including age, sex, presence of ventilatory support, presence of hemodynamic support, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores and RIFLE criteria at admission, and death within 28 days were registered. Five blood samples were collected from all patients at admission and the 24th, 48th, 72nd and 120th h for NT-proBNP measurements. In addition to NT-proBNP, procalcitonin and lactate levels were also measured at admission.

For the determination of NT-proBNP concentrations electrochemiluminescent immunoassay (ElecSys 2010, Roche Diagnostics, Mannheim, Germany) was used. The analytic range for this test was 30–35 000 pg/ml and the coefficient of variance was below 3%.

Statistical analysis

The area under the ROC curve quantifies the diagnostic accuracy of a test. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test [19]. An area of 0.75 represents a fair test of accuracy. For this study, the area under the ROC curve which is expected to be significant was 0.75. The value of the area under the curve for the null hypothesis was 0.5. Type I error was defined as $\alpha = 0.05$ and type II error $\beta = 0.10$. Hence, the sample size for each group was calculated as 25.

Metric continuous variables between groups were compared with Student’s t-test or the Mann-Whitney U test after the Kolmogorov-Smirnov test was applied for normality and variables were presented as mean ± SD or median (25th–75th percentiles). Categorical variables between groups were compared with $\chi^2$ or Fisher’s exact test and variables were presented as percentages (%). For the trend analysis within groups, the repeated measures analysis of variance test or Friedman variance analysis test were used. Multiple pairwise comparisons were made with Bonferroni correction within groups. Receiver-operating characteristic (ROC) curves were plotted to define the prognostic performance and the cutoff value of NT-proBNP, SOFA score, lactate, and procalcitonin, which provides the best sensitivity and specificity in both non-septic and septic groups. Results are presented as area under the curve (AUC) and 95% confidence intervals. $P$-value < 0.05 was considered statistically significant for all tests. AUC for different parameters are compared with the Hanley and McNeil method.

Also a multivariate logistic regression model was fitted to detect the independent predictors of ICU mortality. Variables that were significant in the univariate model were tested further with multivariate logistic regression analysis for independent contribution to ICU mortality.

All statistical analyses were performed with MedCalc version 12.2.1.0 (MedCalc Software bvba, Mariakerke, Belgium).
Results

In total 50 patients were enrolled in this study. In the non-septic group, postoperative patients of abdominal and orthopedic surgery were in the majority. In the septic group, the patients were in sepsis mainly secondary to respiratory or urinary tract infection. Clinical characteristics of the patients at admission are shown in Table I. Age and gender of the patients, presence of ventilatory treatment and RIFLE criteria at admission were similar in groups. Septic patients had higher APACHE II (19 (16.00–24.25) vs. 16 (13.00–18.25)), and SOFA (8 (5–10) vs. 6 (4–7)) scores compared to non-septic patients (p < 0.05). Lactate levels were similar between groups. Procalcitonin levels were also higher in septic patients (3.33 (1.06–10.96) vs. 0.46 (0.26–1.01) ng/ml) and more patients required vasopressors in the septic group (9 vs. 2), (p < 0.05). Nine vs. fourteen patients died in non-septic and septic groups, respectively (p = 0.26) (Table I).

Receiver-operating characteristic curves of SOFA scores, procalcitonin and lactate levels were drawn for both groups to determine the prognostic accuracy. In the non-septic group, none of these parameters correlated significantly with mortality at admission. For the septic group, procalcitonin levels were significantly correlated with mortality at admission. Receiver-operating characteristic curve comparison for procalcitonin and NT-pro-BNP in the septic group was statistically insignificant (Table II, Figure 1 A and 2 A).

Table I. Clinical characteristics of patients

| Parameter                  | Non-septic group (n = 25) | Septic group (n = 25) | P-value |
|----------------------------|---------------------------|-----------------------|---------|
| Age [years]*               | 74 (64.50–79.25)          | 63 (34.75–76.50)      | 0.06    |
| Gender (male) (%)          | 12 (48%)                  | 15 (60%)              | 0.08    |
| APACHE II*                 | 16 (13.00–18.25)          | 19 (16.00–24.25)      | 0.03    |
| SOFA*                     | 6 (4–7)                   | 8 (5–10)              | 0.01    |
| RIFLE†                     | 21/1/2/1/0/0              | 16/2/1/6/0/0          | 0.18    |
| Mean arterial pressure [mm Hg]* | 102.60 ±13.42             | 91.53 ±16.88          | 0.013   |
| Ventilator treatment (%)   | 16/25 (64%)               | 20/25 (80%)           | 0.34    |
| Hemodynamic support (%)    | 2/25 (8%)                 | 9/25 (36%)            | 0.04    |
| 28-day mortality (%)       | 9/25 (36%)                | 14/25 (56%)           | 0.26    |
| Procalcitonin [ng/ml]*     | 0.46 (0.26–1.01)          | 3.33 (1.06–10.96)     | < 0.001 |
| Lactate [mEq/l]*           | 1.260 (0.927–1.597)       | 1.060 (0.942–1.477)   | 0.57    |

NT-proBNP [pg/ml]*:

| Variable                  | Non-septic group (n = 25) | Septic group (n = 25) | P-value |
|----------------------------|---------------------------|-----------------------|---------|
| Admission                  | 2968.55 ±2558.39          | 9828.15 ±11272.61     | 0.006   |
| 24th h                     | 3223.16 ±2691.93          | 9200.89 ±10849.39     | 0.11    |
| 48th h                     | 3449.30 ±2954.54          | 9915.78 ±11262.94     | 0.06    |
| 72nd h                     | 3635.25 ±3350.37          | 10768.24 ±11527.76    | 0.02    |
| 120th h                    | 3820.42 ±3776.92          | 11133.06 ±11940.43    | 0.03    |

Table II. Areas under the ROC for NT-proBNP, SOFA, procalcitonin, lactate for groups at admission

| Variable   | Non-septic group (n = 25) | Septic group (n = 25) | P-value |
|------------|---------------------------|-----------------------|---------|
| NT-proBNP  | 0.556 0.345–0.752          | 0.740 0.528–0.893     |         |
| SOFA       | 0.611 0.397–0.798          | 0.692 0.477–0.859     |         |
| Procalcitonin | 0.549 0.339–0.746        | 0.760 0.548–0.906     |         |
| Lactate    | 0.694 0.480–0.861          | 0.659 0.444–0.835     |         |

*Median (25th–75th percentile), †RIFLE – numbers represent normal, risk, injury, failure, loss and end stage for RIFLE criteria respectively, ‡mean ± SD.
Comparison of prognostic value of N-terminal pro-brain natriuretic peptide in septic and non-septic intensive care patients

Figure 1. Receiver-operating characteristic (ROC) curves for NT-proBNP of the septic group of patients. Areas under the ROC for each measurement hour are as follows (AUC (95% CI) (p)).

A – Admission: sensitivity: 54.5, specificity: 92.9, criterion ≤ 1692,

B – 24th h: sensitivity: 90.9, specificity: 57.1, criterion ≤ 5983

C – 48th h: sensitivity: 63.6, specificity: 85.7, criterion ≤ 2959

D – 72nd h: sensitivity: 72.7, specificity: 78.6, criterion ≤ 4025

E – 120th h: sensitivity: 90.9, specificity: 71.4, criterion ≤ 6892

Sensitivity: 63.6
Specificity: 85.7
Criterion: ≤ 2959

Sensitivity: 72.7
Specificity: 78.6
Criterion: ≤ 4025

Sensitivity: 90.9
Specificity: 71.4
Criterion: ≤ 6892
Figure 2. Receiver-operating characteristic curves for NT-proBNP of the non-septic group of patients. Areas under the ROC for each measurement hour are as follows (AUC (95% CI) (p)).

- **A** – Admission: 0.556 (0.345–0.752), (p = 0.65), sensitivity: 31.2, specificity: 88.9, criterion ≤ 640;
- **B** – 24th h: 0.639 (0.424–0.819) (p = 0.26),
- **C** – 48th h: 0.674 (0.459–0.846) (p = 0.14),
- **D** – 72nd h: 0.715 (0.501–0.876) (p = 0.07),
- **E** – 120th h: 0.750 (0.538–0.900) (p = 0.02), respectively

**Sensitivity:** 56.2
**Specificity:** 77.8
**Criterion:** ≤ 1822

**Sensitivity:** 75.8
**Specificity:** 66.7
**Criterion:** ≤ 3974

**Sensitivity:** 75.0
**Specificity:** 77.8
**Criterion:** ≤ 3172

---

Namik Ozcan, Ayse Ozcan, Cetin Kaymak, Hulya Basar, Mustafa Kotanoglu, Bektas Kose
Comparison of prognostic value of N-terminal pro-brain natriuretic peptide in septic and non-septic intensive care patients

Receiver-operating characteristic curves for NT-proBNP were also drawn for every 24 h for the prediction of ICU mortality in each group. In the septic group, area under the ROC curve was significantly different from 0.5 on each day, indicating that the correlation between mortality and the level of the NT-proBNP in septic patients was significant at each measurement time starting from admission (Figure 1). In the non-septic group the AUC showed a significant correlation between mortality and the level of NT-proBNP only at the 120th h (Figure 2).

In the septic group NT-proBNP levels of nonsurvivors were significantly higher than the survivors in the entire cohort. In addition, in the septic group, NT-proBNP levels of the nonsurvivors increased significantly from admission to the 120th h ($p < 0.001$), while the NT-proBNP levels of the survivors did not change ($p = 0.40$) (Figure 3).

In the non-septic group, the NT-proBNP levels were similar between survivors and nonsurvivors except at the 120th h ($p = 0.04$). Similar to the septic group, nonsurvivors in this group displayed an increasing trend of NT-proBNP levels ($p < 0.001$), while the NT-proBNP levels did not increase throughout the study in survivors ($p = 0.25$) (Figure 4).

A logistic regression model for detection of independent ICU mortality predictors was established, but the sample size of a single group was insufficient. For the purpose of this analysis septic and non-septic groups are combined. Univariate analysis included admission NT-proBNP, procalcitonin and lactate levels, age, APACHE II, and SOFA scores. In univariate logistic regression analysis, significant predictors ($p < 0.05$) for ICU mortality were NT-proBNP, lactate levels and APACHE II score. They were entered into a multiple stepwise logistic-regression model (model significance $p = 0.0021$). The only independent predictor of ICU mortality was admission NT-proBNP levels (coefficient: 0.00011, $p = 0.045$).

**Discussion**

The present study shows that NT-proBNP is an independent predictor of mortality in the ICU and high levels measured at admission to the ICU are significantly correlated with mortality in septic patients. In non-septic patients repeated measurements and progressive increase in the NT-proBNP levels may correlate with mortality in the ICU.

NT-proBNP is synthesized in response to increased ventricular wall stress. Its level increases in patients with heart failure, pulmonary embolism, sepsis, shock and renal failure [20–25]. Sepsis-related cytokines lead to myocardial dysfunction and stimulate NT-proBNP excretion in patients with sepsis or septic shock [15]. NT-proBNP is excreted by the kidneys, and renal failure also increases the level of NT-proBNP [26]. Besides hypoxia, proinflammatory cytokines, lung injury, excessive fluid resuscitation, vasopressors and positive pressure ventilation also increase BNP levels [27–30]. It is a nonspecific prohormone and myocardial dysfunction due to any kind of severe illness which lead the patient to the ICU increase its level [10, 14, 21–23, 26, 29–31].

In most of the previous studies reporting the correlation between mortality and NT-proBNP levels, patients were septic, on vasopressors or required mechanical ventilation [6, 10, 12–16, 22, 23, 31]. Our patients in the septic group were consistent with the patients in these studies. APACHE II and SOFA scores and procalcitonin levels were significantly higher and more patients required vasopressor therapy in this group. In septic patients, the area under the ROC curve of 28-day mortality for NT-proBNP was 0.74 at admission and increased to 0.85 at the 120th h (Figure 1). However, no significant correlation was found between the level of NT-proBNP and mortality at admission to the ICU for non-septic patients. The fifth measurement at the 120th h showed a significant correla-
tion and the area under the ROC curve was 0.750 (Figure 2) in non-septic patients.

The prognostic power of NT-proBNP is controversial in an unselected, general ICU population. For instance, Cuthbertson et al. [12] stated that cardiac dysfunction is thought to be an important prognostic factor for poor outcome but B-type natriuretic peptide levels do not predict outcome accurately in all intensive care patients. Also Almog et al. [13] reported that NT-proBNP levels are highly variable among critically ill patients. High levels of NT-proBNP level at admission are an independent predictor of mortality. Many factors characterizing the patients may affect the level of NT-proBNP. This may explain the different cut-off values in different studies with different patient characteristics [10, 22, 31, 32]. Most of the studies in the literature are composed of septic patients. To our knowledge, this is the first study that compares the prognostic value of NT-proBNP levels in septic and non-septic ICU patients. APACHE II, SOFA scores and procalcitonin levels and vasopressor requirements were higher in the septic group. Analysis of levels of NT-proBNP in these septic and non-septic patients resulted in different AUCs and cut-off values. The only similarity between these groups was the significant increase in NT-proBNP levels in the nonsurvivors of both groups. Survivors in both groups showed a steady level of NT-proBNP level in the cohort. These findings are also consistent with those of Varpula et al. [10], Cuthbertson et al. [12] and Roch et al. [31].

In non-septic patients NT-proBNP levels were low at the beginning, and no significant correlation between mortality and NT-proBNP levels was observed. In nonsurvivors NT-proBNP levels increased and the correlation with mortality became significant on the fifth day. For the patients with low levels of NT-proBNP at admission, similarly as the non-septic group of this study, repeated measurements may be useful to catch the NT-proBNP increase during the ICU stay. Consistent with this observation, Park et al. [18] suggested repeated measurements to observe the percent change in NT-proBNP, which may provide prognostic accuracy in patients with septic shock.

This study had some limitations. The number of patients in each group was limited to 25. Bigger groups might provide more clear-cut results. Although we excluded patients with heart failure at admission, ventricular dysfunction due to severe illness (sepsis and systemic inflammation) also cannot be excluded. In addition, if we had measured levels of inflammatory cytokines, we might have detected a correlation between septic cardiomyopathy and NT-proBNP levels.

We conclude that NT-proBNP is an independent predictor of mortality in the ICU and the level at admission is well correlated with 28-day mortality in septic ICU patients. However, single measurement of NT-proBNP levels in non-septic patients does not correlate with the 28-day mortality. Repeated measurements and the increasing trend of the NT-proBNP levels may show a correlation with mortality in non-septic intensive care patients with low levels of NT-proBNP at admission.

Conflict of interest

The authors declare no conflict of interest.

References

1. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998; 339: 321-8.
2. Hall C. Essential biochemistry and physiology of (NT-pro) BNP. Eur J Heart Fail 2004; 15: 257-60.
3. Richards AM, Lainchbury JG, Troughton RW, Espiner EA, Nicholls MG. Clinical applications of B-type natriuretic peptides. Trends Endocrinol Metab 2004; 15: 170-4.
4. Masson S, Latini R, Anand IS, et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: theValsartan Heart Failure (Val-Heft) data. Clin Chem 2006; 52: 1528-38.
5. De Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. Lancet 2003; 362: 316-22.
6. Januzzi JL, Camargo CA, Anand IS, et al. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. Am J Cardiol 2005; 95: 948-54.
7. Troughton RW, Frampton CM, Yandle TG, Espiner EA, Nicholls MG, Richards AM. Treatment of heart failure guided by plasma aminoterminal brain natriuretic peptide (N-BNP) concentrations. Lancet 2000; 355: 1126-30.
8. Burke MA, Cotts WG. Interpretation of B-type natriuretic peptide in cardiac disease and other comorbid conditions. Heart Fail Rev 2007; 12: 23-36.
9. Fedor M, Lombardo E, Testa M, Avogadri E, Piccolo S, Vado A. Prognostic factors of mid-term clinical outcome in congestive heart failure patients discharged after acute decompensation. Arch Med Sci 2012; 8: 462-70.
10. Varpula M, Pulkkki K, Karlsson S, Ruokonen E, Pettila V. Predictive value of N-terminal pro-brain natriuretic peptide in severe sepsis and septic shock. Crit Care Med 2007; 35: 1277-83.
11. Berendes E, Van Aken H, Raufhake C, Schmidt C, Assmann G, Walter M. Differential secretion of atrial and brain natriuretic peptide in critically ill patients. Anesth Analg 2001; 93: 676-82.
12. Cuthbertson BH, Patel RR, Croal BL, et al. B-type natriuretic peptide and the prediction of outcome in patients admitted to intensive care. Anaesthesia 2005; 60: 16-21.
13. Almog Y, Novack V, Megralishvilli R, et al. Plasma level of N-terminal pro-brain natriuretic peptide as a prognostic marker in critically ill patients. Anesth Analg 2006; 102: 1809-15.
14. Meyer B, Huelsmann M, Wexberg R et al. N-terminal proBNP peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. Crit Care Med 2007; 35: 2268-73.
15. Shah KB, Nolan MM, Rao K, et al. The characteristics and prognostic importance of NT-proBNP concentrations in critically ill patients. Am J Med 2007; 120: 1071-7.
Comparison of prognostic value of N-terminal pro-brain natriuretic peptide in septic and non-septic intensive care patients

16. Kotanidou A, Karsalikos P, Tzanela M, et al. Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. Shock 2009; 31: 342-7.

17. De Geer L, Fredrikson M, Oscarsson A. Amino-terminal pro-brain natriuretic peptide as a predictor of outcome in patients admitted to intensive care. A prospective observational study. Eur J Anaesthesiol 2012; 29: 275-9.

18. Park BH, Park MS, Kim YS, et al. Prognostic utility of changes in n-terminal pro-brain natriuretic peptide combined with sequential organ failure assessment scores in patients with acute lung injury/acute respiratory distress syndrome concomitant with septic shock. Shock 2011; 36: 109-14.

19. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. Clin Chem 1993; 39: 561-7.

20. Kucher N, Printzen G, Doernhoefer T, Windecker S, Meyer B, Hess OM. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. Circulation 2003; 107: 1576-8.

21. Kucher N, Printzen G, Goldhaber SZ. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. Circulation 2003; 107: 2545-7.

22. 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: 527-34.

23. 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: 1643-7.

24. McCullough PA, Duc P, Omland T, et al. Breathing Not Properly Multinational Study Investigators. B-type natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the Breathing Not Properly Multinational Study. Am J Kidney Dis 2003; 41: 571-9.

25. Franz M, Woloszczuk W, Hoenel WH. Plasma concentration and urinary excretion of N-terminal proatrial natriuretic peptides in patients with kidney diseases. Kidney Int 2001; 59: 1928-34.

26. Goel D, Schouten Q, Boersma E, et al. Influence of renal function on the usefulness of N-terminal pro-B-type natriuretic peptide as a prognostic cardiac risk marker in patients undergoing noncardiac vascular surgery. Am J Cardiol 2008; 101: 122-6.

27. Weidemann A, Klomke B, Wagner M, et al. Hypoxia, via stabilization of the hypoxia-inducible factor HIF-1alpha, is a direct and sufficient stimulus for brain-type natriuretic peptide induction. Biochem J 2008; 409: 233-42.

28. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocytic reactions via p38 MAP kinase. J Mol Cell Cardiol 2004; 36: 505-13.

29. Sun JZ, Chen SJ, Li G, Chen YF. Hypoxia reduces atrial natriuretic peptide clearance receptor gene expression in ANP knockout mice. Am J Physiol Lung Cell Mol Physiol 2000; 279: L511-9.

30. Park BH, Kim YS, Chang J, et al. N-terminal pro-brain natriuretic peptide as a marker of right ventricular dysfunction after open-lung approach in patients with acute lung injury/acute respiratory distress syndrome. J Crit Care 2011; 26: 241-8.