Effects of Recombinant Human Brain Natriuretic Peptide in Patients with Acute Pulmonary Embolism Complicated with Right Ventricular Dysfunction Who Underwent Catheter-Directed Therapy

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Summary

Acute pulmonary embolism (PE) remains a significant cause of cardiovascular morbidity and mortality worldwide. Brain natriuretic peptide (BNP) combined with catheter-directed therapy (CDT) may improve right ventricular (RV) dysfunction and stabilize hemodynamics in acute PE.

We retrospectively studied 159 patients with confirmed acute PE who were treated with CDT and admitted to the intensive care unit of our department between September 2016 and May 2020. The patients were divided into the control group and the rhBNP group based on whether to receive recombinant human BNP treatment (rhBNP) or not. The basic characteristics of the patients between the control group and the rhBNP group was systematically compared during admission and follow-up. Risk factors for all-cause mortality within 30 days were determined using multivariate logistic regression analysis.

Respiratory rate was found to be significantly lower in the rhBNP group than in the control group. Patients in the rhBNP group had significantly lower levels of white blood cell, C-reactive protein (CRP), D-dimers, troponin I, creatinine, and N-terminal (NT)-proBNP compared with those in the control group. Levels of tricuspid annular plane systolic excursion were significantly higher in the rhBNP group than in the control group. The percentage of patients with rehospitalization readmission due to PE differed significantly between the control group and the rhBNP group. On the basis of the multivariate regression analysis, CRP, creatinine, troponin I, and NT-proBNP were independent factors of all-cause mortality in 30 days.

rhBNP is effective in the treatment of patients with RV dysfunction caused by acute PE who underwent CDT, which may be an alternative treatment option for improving clinical prognosis.

Key words: Right heart failure, White blood cell, C-reactive protein, D-dimers, Troponin I, Inflammation

Acute pulmonary embolism (PE) remains a significant cause of cardiovascular morbidity and mortality due to right ventricular (RV) dysfunction worldwide.1-4) Patients with acute PE with compromised hemodynamics and right heart strain as diagnosed via pulmonary computed tomography angiography (CTA) may benefit from endovascular treatment. Specifically, patients with acute submassive PE as indicated by evidence of cardiac ischemia [elevated troponin and brain natriuretic peptide (BNP)] and right heart strain are candidates for endovascular treatment or systemic thrombolysis.5) Although systemic thrombolysis may reduce mortality, it is also associated with a higher risk of hemorrhagic complications including a 2%-5% risk of hemorrhagic stroke.6) Catheter-directed therapy (CDT) that uses pharmacomechanical methods and low-dose thrombolytic infusion is an alternative to systemic thrombolysis. Recently, CDT has demonstrated efficacy in the treatment of RV dysfunction in trial populations,7) with no increase in bleeding complications.

It is noteworthy that plasma concentrations of BNP are increased in cases of isolated acute or chronic RV dysfunction.8) Recombinant human BNP (rhBNP) is effective in the treatment of acute or chronic heart failure.9) However, little is known about rhBNP treatment of acute RV dysfunction caused by severe PE. Inflammation is considered a risk factor for venous thromboembolism. The association between inflammatory markers and the severity of acute PE should be explored.10)
A 44-year-old male patient with high clinical suspicion of acute pulmonary embolism (PE). Axial images from a pulmonary arterial phase contrast-enhanced chest computer tomography. A: Bilateral subsegmental thrombus. B: Large, expansile, central thrombus in the right pulmonary artery.

Therefore, this study aims to determine how BNP levels are affected by acute PE with RV dysfunction and to test the clinical effect and prognostic implications of rhBNP in patients who underwent CDT by reducing the level of systemic inflammation.

Methods

Ethics statement: This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution’s human research committee and the study was approved by the Research Ethics Committee of Jiamusi University, China. Informed consent was obtained from each patient.

Study population: We retrospectively studied 159 patients with confirmed acute PE who were treated with CDT and admitted to the intensive care unit of our department between September 2016 and May 2020. Patients were divided into the control group and the rhBNP group based on whether they received rhBNP or not. Patients were included if they had acute massive or submassive PE presenting within 14 days and pulmonary CTA evidence of proximal PE defined as a filling defect in at least one main or lobar pulmonary artery (Figure 1). Massive PE was defined as acute PE with sustained hypotension of systolic pressure < 90 mmHg for at least 15 minutes or requiring inotropic support. Submassive PE was defined as acute PE causing RV dilatation and hypokinesis confirmed on echocardiography or pulmonary CTA, or both, without systemic hypotension. Patients were excluded if they were younger than 18 years, could not tolerate anticoagulant therapy, or had tumor thrombus in the pulmonary arteries.

Catheter-directed therapy: The decision about the ideal therapeutic strategy in an individual patient with acute PE should be made by a PE response team. Massive PE was treated with immediate catheter-directed mechanical or pharmacomechanical thrombectomy using defined modern CDT techniques including catheter-directed fragmentation of PE, intra-clot lytic injection, and aspiration (Figure 2). Submassive PE was treated with catheter-directed thrombolysis via low-dose hourly drug infusion into the clot with recombinant tissue plasminogen activator (0.5-1.0 mg/hour) as a previously described protocol. Thrombolytic drugs were delivered using standard infusion catheters such as the Unifuse (Angiodynamics, Queensbury, NY, USA) or multiside-hole pigtail catheter (Cook, Bloomington, IN, USA). Following completion of CDT, all patients received parenteral anticoagulation as a bridge to warfarin, an injectable anticoagulant as monotherapy, or rivaroxaban.

rhBNP treatment: After CDT, patients in the rhBNP group were given intravenous injection of a loading dose of rhBNP 1.5 μg/kg and they were given intravenous rhBNP 0.015 μg/kg/minute through an infusion pump for 72 hours, with a concentration of 10 μg/mL.

Blood sampling: Blood samples were collected from cubital veins in all patients who were enrolled in the study. N-terminal (NT)-proBNP and troponin I were measured on admission. The level of NT-proBNP in the plasma was measured using an Elecsys NT-proBNP analyzer, a commercially available electrochemiluminescent sandwich immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). C-reactive protein (CRP) levels were measured using a commercially available immunonephelometric kinetic assay (BN ProSpec; Siemens, Tarrytown, NY, USA) using Cardiophase CRP reagents. Other biochemistry measurements were performed using the Jaffe kinetic method on a Hitachi 7600 Autoanalyzer (Hitachi, Ltd., Tokyo, Japan).

Statistical analysis: Quantitative variables were expressed as mean value ± standard deviation, and qualitative variables were expressed as total number and percentage. The independent two-sample t-test or one-way analysis of variance with post hoc Student-Newman-Keuls test was used to assess the differences between multiple sets of data. Categorical variables were also compared using the chi-squared or Fisher’s exact test. Independent predictors of all-cause mortality within 30 days were identified using multivariate logistic regression analyses. Statistical significance was indicated when a two-sided P-value was < 0.05. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).
Figure 2. The process of catheter-directed therapy (CDT) in patients with acute pulmonary embolism (PE). **A, B:** Preliminary digital subtraction pulmonary angiography through a 9-Fr sheath positioned in the pulmonary artery via right internal jugular vein access demonstrates occlusive thrombus in the right pulmonary artery and scattered thrombi in the left pulmonary circulation, with no perfusion to the right lung. **C:** More lobar and segmental branch opacification and greater perfusion to the upper and lower lobes after CDT. **D-F:** Mechanical fragmentation is based on the insertion of a pigtail catheter into the pulmonary arteries via the femoral route.

Results

Baseline characteristics: One hundred and fifty-nine patients (71 men and 88 women) were enrolled. The baseline characteristics and invasive hemodynamic measurements of the control group and the rhBNP group are presented in Tables I, II. There were no significant differences in the baseline characteristics.

Comparison of patients’ characteristics at discharge: Respiratory rate was found to be significantly lower in the rhBNP group than in the control group. Patients in the rhBNP group had significantly lower levels of white blood cell, CRP, D-dimers, troponin I, creatinine, and NT-proBNP compared with those in the control group. Levels of tricuspid annular plane systolic excursion were significantly higher in the rhBNP group than in the control group (Table III).

Thirty days follow-up: During the follow-up period of 30 days, the incidence of readmission due to PE was significantly lower in the rhBNP group than in the control group (Table IV). Following multivariate logistic regression analysis, CRP [odds ratio (OR) = 1.256 (95% confidence interval (CI) 1.104-1.430), \( P = 0.001 \)], creatinine [OR = 1.033 (95% CI 1.002-1.065), \( P = 0.039 \)], NT-proBNP [OR = 1.002 (95% CI 1.001-1.004), \( P = 0.005 \)], and troponin I [OR = 12.952 (95% CI 1.529-109.684), \( P = 0.019 \)] were demonstrated to be independently associated with all-cause mortality within 30 days. NT-proBNP [OR = 1.004 (95% CI 1.001-1.006), \( P = 0.004 \)] was demonstrated to be independently associated with death from PE within 30 days. (Table V).

Discussion

PE is the cause of ≤ 300,000 deaths per year in the US, ranking high among the causes of cardiovascular mortality.\(^{14,15}\) Of these patients, 34% died suddenly or within a few hours of the acute event, before therapy could be initiated or take effect. In recent years, increased use of more effective therapies and interventions, and possibly better adherence to guidelines,\(^{16,17}\) has most likely exerted a significant positive effect on the prognosis of PE.

Acute RV dysfunction with resulting low systemic output is the leading cause of death in patients with high-risk PE. Experimental studies suggest that aggressive volume expansion is of no benefit and may even worsen RV function.\(^{18}\) The principles of acute right heart failure management have been reviewed in a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology.\(^{19}\) Systemic thrombolysis leads to faster improvements in pulmonary obstruction, pulmonary artery pressure (PAP), and pulmonary vascular resistance (PVR) in patients with PE, compared with unfractionated heparin alone; these improvements are accom-
Table I. Baseline Characteristics of Patients with Acute Pulmonary Embolism and Right Ventricular Dysfunction

|                      | rhBNP group (n = 74) | Control group (n = 85) | P-value |
|----------------------|----------------------|------------------------|---------|
| Age, years           | 60.89 ± 11.96        | 61.88 ± 10.40          | 0.577   |
| Men, n (%)           | 31 (41.89)           | 40 (47.06)             | 0.311   |
| Symptoms, n (%)      |                      |                        |         |
| Dyspnea              | 53 (71.62)           | 56 (65.88)             | 0.273   |
| Chest pain           | 17 (22.97)           | 24 (28.24)             | 0.283   |
| Syncope              | 4 (5.41)             | 5 (5.88)               | 0.587   |
| Shock                | 7 (9.46)             | 10 (11.76)             | 0.418   |
| Vital signs          |                      |                        |         |
| Systolic blood pressure, mmHg | 110.84 ± 12.95   | 108.45 ± 11.98          | 0.229   |
| Heart rate, beats/min | 91.43 ± 7.37        | 92.25 ± 6.87           | 0.472   |
| Respiratory rate, breaths/minute | 22.84 ± 3.72   | 22.92 ± 4.69           | 0.907   |
| Diagnosis, n (%)     |                      |                        |         |
| Pulmonary CTA        | 54 (72.97)           | 64 (75.29)             | 0.439   |
| Echocardiography     | 20 (27.03)           | 21 (24.71)             | 0.439   |
| Serum values         |                      |                        |         |
| WBC, × 10^9/L        | 13.36 ± 4.76         | 14.13 ± 4.00           | 0.267   |
| CRP, mg/L            | 23.30 ± 12.85        | 26.12 ± 10.80          | 0.135   |
| D-dimers, µg/L       | 3416.30 ± 2194.04    | 3385.69 ± 1955.79      | 0.926   |
| Creatinine, µmol/L   | 121.19 ± 43.52       | 121.86 ± 38.33         | 0.918   |
| NT-proBNP, pg/mL     | 3825.14 ± 753.41     | 3734.92 ± 580.90       | 0.396   |
| Troponin I, µg/L     | 1.20 ± 0.67          | 1.22 ± 0.74            | 0.840   |
| Serum sodium, mmol/L | 142.18 ± 1.54        | 142.25 ± 0.32          | 0.687   |
| Echocardiographic parameters |           |                        |         |
| RV diameter, mm      | 39.24 ± 6.73         | 39.58 ± 7.71           | 0.771   |
| RV hypokinesis, n (%)| 53 (71.62)           | 64 (75.29)             | 0.365   |
| RVSP, mmHg           | 48.11 ± 10.79        | 44.66 ± 11.48          | 0.054   |
| TAPSE, cm            | 2.05 ± 0.85          | 2.06 ± 0.75            | 0.960   |
| Deep-vein thrombosis, n (%) | 45 (60.81)   | 54 (63.53)             | 0.385   |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. WBC indicates white blood cell; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; CTA, computed tomography angiography; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; and RVSP, right ventricular systolic pressure.

Table II. Invasive Hemodynamic Measurements in Patients from the Catheter-directed Therapy

|                      | rhBNP group (n = 74) | Control group (n = 85) | P-value |
|----------------------|----------------------|------------------------|---------|
| Pulmonary artery systolic pressure, mmHg | 42.95 ± 15.26       | 41.95 ± 11.95          | 0.647   |
| Pulmonary artery diastolic pressure, mmHg | 17.57 ± 8.60        | 17.55 ± 6.71           | 0.990   |
| Pulmonary artery mean pressure, mmHg     | 25.27 ± 7.79        | 24.31 ± 4.64           | 0.338   |
| Right atrial mean pressure, mmHg         | 5.89 ± 3.43         | 6.16 ± 2.65            | 0.573   |
| Right ventricular mean pressure, mmHg    | 16.61 ± 7.13        | 17.69 ± 5.28           | 0.273   |
| Pulmonary arterial oxygen saturation, %  | 64.61 ± 7.54        | 64.34 ± 4.18           | 0.779   |
| Cardiac output, L/minute                 | 5.13 ± 1.31         | 5.28 ± 1.33            | 0.498   |
| Cardiac index, L/minute/m²               | 2.81 ± 0.80         | 2.78 ± 0.97            | 0.821   |
| Pulmonary vascular resistance, wood      | 3.00 ± 2.07         | 3.17 ± 1.71            | 0.549   |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. WBC indicates white blood cell; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; CTA, computed tomography angiography; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; and RVSP, right ventricular systolic pressure.

Conversely, medication is still the cornerstone of the treatment of RV dysfunction caused by acute PE. Studies have demonstrated that pathological BNP levels are frequently found in patients with RV dysfunction in acute PE. BNP is secreted mainly from the cardiac ventricles in response to volume expansion and pressure overload. Acute left ventricle (LV) dysfunction leads to a rapid increase in plasma BNP level. In published studies, plasma pro-BNP and BNP levels seem to be predictive of adverse clinical outcome in patients with acute PE. Therefore, rhBNP may be effective in the treatment of acute LV dysfunction through the mechanism of reducing pulmonary artery wedge pressure, which has been shown

Companied by a reduction in RV dilation on echocardiography. However, systemic thrombolysis is accompanied by a significant risk of intracranial hemorrhage of 2% and general major hemorrhage of up to 20%. CDT of acute PE is gaining increasing interest. The rationale behind the removal of the thromboembolic burden in the pulmonary arterial circulation relates to improvement of RV impairment in the setting of elevated PVR and stabilization of the hemodynamics in the acute setting. Data from two prospective cohort studies and a registry with a total of 352 patients, support the improvement in RV function, lung perfusion, and PAP in patients with intermediate- or high-risk PE using systemic thrombolysis.
### Table III. Comparison of Patients’ Characteristics at Discharge

| Feature                      | rhBNP group (n = 74) | Control group (n = 85) | P-value |
|------------------------------|----------------------|------------------------|---------|
| Vital signs                  |                      |                        |         |
| Systolic blood pressure, mmHg| 109.27 ± 12.46       | 108.16 ± 14.09         | 0.603   |
| Heart rate, beats/minute     | 85.54 ± 3.79         | 86.24 ± 6.83           | 0.439   |
| Respiratory rate, breaths/minute | 18.89 ± 1.65       | 20.69 ± 4.84           | 0.003   |
| Serum values                 |                      |                        |         |
| WBC, × 10^9/L                | 8.24 ± 2.12          | 10.74 ± 4.16           | < 0.001 |
| CRP, mg/L                    | 9.47 ± 2.12          | 16.23 ± 7.97           | < 0.001 |
| D-dimers, μg/L               | 1559.77 ± 735.23     | 2564.95 ± 1622.31      | < 0.001 |
| Creatinine, μmol/L           | 109.70 ± 29.22       | 134.07 ± 59.75         | 0.002   |
| NT-proBNP, pg/mL             | 396.38 ± 143.57      | 1131.52 ± 627.02       | < 0.001 |
| Troponin I, μg/L             | 0.200 ± 0.154        | 0.781 ± 0.309          | < 0.001 |
| Serum sodium, mmol/L         | 144.07 ± 3.92        | 144.52 ± 3.81          | 0.467   |
| Echocardiographic parameters |                      |                        |         |
| RV diameter, mm              | 36.58 ± 6.26         | 38.95 ± 9.34           | 0.067   |
| RV hypokinesis, n (%)        | 57 (77.03)           | 74 (87.06)             | 0.143   |
| RVSP, mmHg                   | 40.85 ± 7.61         | 40.02 ± 7.29           | 0.485   |
| TAPSE, cm                    | 3.71 ± 0.77          | 3.30 ± 0.78            | 0.001   |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. WBC indicates white blood cell; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; and RVSP, right ventricular systolic pressure.

### Table IV. In-Hospital and 30-Day Outcomes

| Feature, n (%)                           | rhBNP group (n = 74) | Control group (n = 85) | P-value |
|------------------------------------------|----------------------|------------------------|---------|
| In-hospital                               |                      |                        |         |
| All-cause mortality                       | 6 (8.11)             | 13 (15.29)             | 0.221   |
| Death from PE                             | 4 (5.41)             | 8 (9.41)               | 0.384   |
| Within 30 days                            |                      |                        |         |
| All-cause mortality                       | 8 (9.41)             | 15 (17.65)             | 0.263   |
| Death from PE                             | 6 (8.11)             | 10 (11.76)             | 0.599   |
| Rehospitalization associated with PE      | 7 (9.46)             | 22 (25.88)             | 0.008   |
| New DVT within 30 days                    | 7 (9.46)             | 9 (10.59)              | 0.990   |

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. DVT indicates deep-vein thrombosis; and PE, pulmonary embolism.

### Table V. Multivariate Logistic Regression Analysis for All-Cause Mortality and Death from PE Within 30 Days

| Feature                      | All-cause mortality Odds ratio (95% CI) | P-value | Death from PE Odds ratio (95% CI) | P-value |
|------------------------------|------------------------------------------|---------|-----------------------------------|---------|
| WBC                          | 1.116 (0.894–1.392)                      | 0.333   | 1.214 (0.987–1.493)               | 0.066   |
| CRP                          | 1.256 (1.104–1.430)                      | 0.001   | 1.017 (0.989–1.159)               | 0.092   |
| D-dimers                     | 1.000 (1.000–1.001)                      | 0.208   | 1.000 (1.000–1.001)               | 0.784   |
| Creatinine                   | 1.033 (1.002–1.065)                      | 0.039   | 1.006 (0.983–1.030)               | 0.594   |
| NT-proBNP                    | 1.002 (1.001–1.004)                      | 0.005   | 1.004 (1.001–1.006)               | 0.004   |
| Troponin I                   | 12.952 (1.529–109.684)                   | 0.019   | 3.584 (0.926–13.869)              | 0.064   |
| Respiratory rate             | 0.995 (0.831–1.331)                      | 0.960   | 0.820 (0.641–1.049)               | 0.114   |
| TAPSE                        | 1.074 (0.403–2.864)                      | 0.887   | 0.846 (0.313–2.228)               | 0.742   |
| Pulmonary artery mean pressure| 0.881 (0.764–1.016)                      | 0.082   | 1.022 (0.889–1.175)               | 0.760   |

PE indicates pulmonary embolism; CI, confidence interval; WBC, white blood cell; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; and TAPSE, tricuspid annular plane systolic excursion.

The therapeutic effect of rhBNP in the clinical management of cardiac diseases is well recognized, as well as its ability to exert anti-inflammatory activity in various organs. rhBNP can increase the production of nitric oxide, which regulates the inflammatory factors, as well as reduce acute lung injury in animal models. In our study, CRP levels in the rhBNP group were significantly reduced, and CRP was one of the independent causes of all-cause mortality within 30 days. Several studies confirmed the inflammatory response in acute PE, suggesting the potential value of inflammatory markers in the diagnosis and prognosis in such cases. CRP was extensively studied in venous thromboembolism and had a sensitivity ranging...
60% and 100% at the level between 5 and 10 mg/L and specificity varying between 52% and 78%.16 Several studies reported that CRP had a sensitivity of 100% for excluding acute PE.17-19 It was also found to have a prognostic value where it is associated with RV dysfunction, a predictor of worse outcomes in acute PE.20-23 Inflammation activation was directly related to the extent of both impairment of cardiac function and neurohormonal activation. CRP levels were inversely correlated with ejection fraction and directly correlated with BNP levels.24 In a word, rhBNP showed anti-inflammatory and protective effects on RV dysfunction in acute PE.

Our results revealed that rhBNP significantly decreased the serum concentrations of Tnl and NT-proBNP at discharge and incidence of readmission at follow-up. BNP is a natural factor against cardiac remodeling that regulates the levels of cytokines and inflammatory factors through regulating the expression of fibrosis genes.25 In addition, BNP selectively expands coronary and lung circulation, increases coronary blood flow, and reduces the consumption of myocardial oxygen.26 Thus, we suspected that administration of rhBNP could further improve myocardial perfusion, limit myocardial impaired size, ameliorate cardiac dysfunction, and postpone ventricular remodeling in patients with PE undergoing CDT.

The present study has some limitations. First, the number of patients was relatively small. Second, there is a possibility of significant referral bias because of the retrospective and single-center design of the study. Third, data on long-term events and follow-up were relatively insufficient and are planned to be included in a future study.

In conclusion, rhBNP is effective in the treatment of patients with RV dysfunction caused by acute PE who underwent CDT, which may be an alternative treatment option for improving clinical prognosis.

Disclosure

Conflicts of interest: None.

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