

# Effects of Recombinant Human Brain Natriuretic Peptide in Patients of Chronic Thromboembolic Pulmonary Hypertension with Chronic Kidney Disease Who Underwent Balloon Pulmonary Angioplasty

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## Research Article

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# Abstract

## Background

Chronic thromboembolic pulmonary hypertension (CTEPH) leads to impairment of pulmonary hemodynamics, triggers secondary right heart dysfunction, regularly accompanied by systemic malperfusion, and subsequently alter glomerular filtration rates (GFR). Chronic kidney disease (CKD) may also adversely affect CTEPH prognosis. This study aimed to assess how Brain natriuretic peptide (BNP) combined with balloon pulmonary angioplasty (BPA) improve right heart hemodynamics and estimated GFR (eGFR) of CKD in CTEPH patients.

## Methods

We retrospectively studied 47 patients with confirmed CTEPH with CKD who were treated with BPA and admitted to the intensive care unit between December 2012 and September 2020. The patient was divided into two groups based on whether to receive recombinant human brain natriuretic peptide treatment (rhBNP). The information of patients between two groups was systematically compared in hospital and follow up. eGFR were assessed at several time points.

## Results

For rhBNP group, eGFR was significantly higher in the two periods of Prior to last BPA and 6-month follow-up. A significantly higher  $\Delta$  eGFR from baseline to follow-up was observed. There was significant difference on levels of troponin I, NT-proBNP, and right ventricle diameter at follow-up.

## Conclusion

rhBNP combined BPA therapy improves pulmonary and systemic hemodynamics, with positive effects on renal function, which maybe an alternative treatment option for improving clinical outcomes.

## Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) has a poor prognosis secondary to surviving acute pulmonary embolism [1]. The persistence of thrombotic material leads to obstruction of the pulmonary arteries, which impairment of pulmonary hemodynamics and triggers secondary right heart dysfunction, regularly

accompanied by systemic malperfusion [2]. The currently established therapy is pulmonary endarterectomy (PEA), a potentially curative approach [1]. However, in up to one third of patients, PEA is not feasible and not indicated, mostly due to the presence of peripheral lesions [3]. For these patients, balloon pulmonary angioplasty (BPA) is recommended as an emerging interventional treatment option [4].

Chronic kidney disease (CKD) is a frequent comorbidity in patients suffering from right heart dysfunction due to pulmonary arterial hypertension [5, 6]. It exists complex bilateral interaction of renal and cardiac function and is suggested to be the underlying mechanism of renal failure in pulmonary arterial hypertension [7]. Elevated NT-proBNP concentrations in CTEPH patients undergoing BPA have proven to be mostly reversible, except in patients developing chronic right heart failure [8]. Meanwhile, impaired renal function with a decreased glomerular filtration rate (GFR) leads to accumulation of NT-proBNP and might therefore hamper its prognostic utility [9, 10]. Recombinant human brain natriuretic peptide treatment (rhBNP) is effective in the treatment of renal dysfunction in patients with acute heart failure following myocardial infarction [11]. However, little is known about treatment of rhBNP on right heart failure and renal dysfunction caused by CTEPH.

It could be speculated that both, the improvement of systemic hemodynamics and the repetitive administration of rhBNP might improve renal function in CTEPH patients undergoing BPA. The aim of this study is, therefore, to test clinical effect of rhBNP in patients of CTEPH with CKD who underwent BPA.

## **Materials And Methods**

### **Study population**

The present study retrospectively included 47 patients with confirmed CTEPH with CKD who were treated with BPA and admitted to the intensive care unit between December 2012 and September 2020.

Suggested pre- and post-procedural management of the patients was recently published [12]. In brief, clinical examination, echocardiography, 12-lead electrocardiogram, laboratory tests, 6-minute walk tests, computed tomography angiography, right-heart catheterization and pulmonary angiography were assessed for all patients. The final diagnosis of CTEPH was made according to the current guidelines

[13]. All patients were presented in an interdisciplinary CTEPH conference to define the therapeutic concept. BPA was performed as a staged procedure according to standard clinical practice by a dedicated BPA team (interventional radiologist, cardiologist and thoracic surgeon). The interval between each BPA sessions is about 4-8 weeks. Prior to the next BPA procedure, follow-up examinations were performed that were adjusted to the individual requirements of each patient, always including reevaluation of clinical status and laboratory findings. Finally, an in-hospital follow-up examination was performed 6 months after the last BPA procedure.

### **Right heart catheterization**

Right heart catheterization (RHC) was performed as a part of the diagnostic work-up [13]. RHC was routinely performed via the right internal jugular vein using a 6F sheath and a standard Swan-Ganz catheter. Medication of the patients was not modified before or during RHC; in particular, no vasoactive agents were administered. All patients received pulmonary hypertension therapy, such as Riociguat, phosphodiesterase-5 or endothelin receptor antagonist, according to RHC assessment.

## Balloon pulmonary angioplasty

BPA was performed as staged procedure under smooth sedation using femoral or jugular access as previously described (Figure 1) [14]. All patients received anticoagulation with rivaroxaban, which was paused for the intervention day (without low molecular weight heparin bridging). During the procedure, patients received heparin intravenously at 100 IU/kg to maintain an activated clotting time (ACT) >250 seconds. A 6F sheath (Terumo, Tokyo, Japan) was placed in the pulmonary artery, and a 6F guiding catheter (JR 4, Dublin, Ireland) was inserted into the pulmonary artery to selectively intubate the obstructed segmental arteries. The guide-wire (Run-through NS-PTCA, Terumo, Tokyo, Japan) was placed into the sub-segmental arterial branches, passing the obstructing endoluminal material. The sub-segmental branches were then dilated by multiple inflations of semi-compliant balloons (Emerge 2.0/15 mm, Boston Scientific, Marlborough, MA). A final fluoroscopy documented the post-procedural morphologic result.

## Blood sampling and laboratory assessment of renal function

Blood samples were collected from cubital veins in all patients who were enrolled in the study. 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). 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).

Venous blood samples for determination of serum creatinine and serum urea were collected in plain tubes at baseline, prior to and after each BPA procedure, and at the 6-month follow-up. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated modification of diet in renal disease formula and was used as the main parameter for the assessment of chronic renal function [15]. CKD was defined as baseline estimated glomerular filtration rate (eGFR) between 15 and 60 mL/min/1.73 m<sup>2</sup> as assessed by the simplified Modification of Diet in Renal Disease (MDRD) formula:  $eGFR = 186.3 (SCr)^{-1.154} (age)^{-0.203}$  (female:  $\times 0.742$ ) [16]. In accordance with the recommendations of the Acute Kidney Injury Network, acute renal failure was defined as an increase of the serum creatinine of  $\geq 0.3$  mg/dL ( $\geq 26.4$  mmol/L) or to  $\geq 150\%$  from baseline [17]. Contrast-induced renal failure usually occurs within 72 h after exposure [18]. Thus, renal biomarkers were measured prior to, 24, 48 and 72 h after the BPA in this study.

## Treatment

Several prevention strategies have been proposed such as low dose of low osmolar contrast media (Visipaque, GE Healthcare Ireland, Dublin, Ireland), hydration, and nephroprotective drugs during hospitalization. All patients who undergo BPA intervention receive 500 mL saline, 20 mg furosemide and 1g potassium chloride once one day prior to a BPA session, once immediately after BPA and once on the

day after the BPA, individually adapted to serum electrolytes if necessary. Patients in the rhBNP group received 0.005 µg/kg/min of rhBNP (Lyophilized Recombinant Human Brain Natriuretic Peptide, Chengdu Nuodikang Biological Pharmaceutical Co. Ltd., China).

## **Statistical analysis**

Quantitative data were expressed as mean value ± standard deviation, while qualitative data were expressed as frequency (percentage). The independent two-sample t-test was used for between-group comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was indicated for two-sided p-values <0.05. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

## **Results**

### **Baseline characteristics**

In total 195 (mean 4/patient) BPA interventions with a treatment of 392 (mean 8/patient) vessels were performed. The most frequent complications after BPA were hemoptysis in 6.4% (3 patients) and reperfusion injury in 2.1% (one patient), and rate of periinterventional acute kidney injury (AKI) was zero. The survival rate in 6-month follow-up was 100%. The median time interval between the first BPA and 6-month follow-up was 317 days.

The baseline characteristics and invasive hemodynamic measurements of two groups are presented in Table 1 and 2. There were no significant differences in the baseline characteristics.

### **Dynamics of renal function during BPA treatment and follow-up**

Dynamics of renal function during BPA treatment and follow-up are shown in Figure 2. There is an upward trend for eGFR from baseline to follow-up between two groups. For rhBNP group, eGFR was significantly higher in the two periods of Prior to last BPA and 6-month follow-up. Patients in rhBNP group had significantly higher  $\Delta$  eGFR from baseline to follow-up, compared to control group (Figure 2).

### **Six months follow-up**

In 6-month follow-up after the last BPA, patients in rhBNP group had significantly lower levels of troponin I, NT-proBNP, and right ventricle diameter compared to control group. Levels of TAPSE was significantly higher in rhBNP group compared to control group (Table 3).

## **Discussion**

The main findings of this study are: (1) rhBNP combined BPA therapy is a safe approach regarding the periprocedural effects on renal function. (2) Among patients suffering from CKD at baseline, renal

function improved after rhBNP combined BPA, which might be related to the improvement of systemic circulation.

In consideration of renal function assessment in CTEPH patients undergoing BPA, procedural aspects need to be further discussed. Nowadays, BPA is recommended as a staged procedure, which includes a sequence of sessions with an interval of 4-8 weeks [19]. This distinctly reduced the rate of reperfusion injury, but increased the number of interventions, the use of radiation and iodine contrast agent. In our study, periinterventional AKI not only has not occurred, but also renal function significantly improved after rhBNP combined BPA. Two reasons were speculated: (1) The stringent periprocedural renal protection have been proposed such as low dose of low osmolar contrast media, hydration, and nephroprotective drugs prior to each BPA. (2) Both rhBNP and BPA therapy could increase effective circulating blood volume and adequate tissue perfusion preserving better renal function.

The frequent coincidence of cardiac diseases and renal dysfunction has been subject to intensive investigations. The chronic impairment of renal function needs to be taken into account as a relevant comorbidity in the context of pulmonary hypertension. The chronic increase in right ventricular afterload may eventually lead to right heart failure that leads to backward failure and triggers venous congestion which further promotes renal failure, the final consequence of which is reduced eGFR [20]. Venous congestion following circulating blood volume reduction has been reported to be the main underlying cause for renal dysfunction [21]. In a cohort of patients suffering from pulmonary arterial hypertension, Bitker et al. [5] reported a correlation of eGFR with cardiac index (CI) at baseline and with right atrial pressure (RAP) within the longitudinal follow-up. After the BPA therapy, improved pulmonary hemodynamics lead to reduced right heart stress, mirrored by decreased NT-proBNP concentrations, which comes along with a relevant decrease of venous congestion and an improvement of renal function [22].

The therapeutic effect of rhBNP in the clinical management of cardiac diseases is well recognized [23]. BNP is a natural factor against cardiac remodeling, and selectively expands coronary and lung circulation, increases coronary blood flow and reduces the consumption of myocardial oxygen [24, 25]. Our results revealed that rhBNP significantly decreased the serum concentrations of Tnl and NT-proBNP in follow-up. Thus, we suspected that administration of rhBNP could further improve myocardial perfusion, limit myocardial impaired size, ameliorate cardiac dysfunction, and postpone ventricular remodeling in CTEPH patients undergoing BPA. This basically supports our findings, that a significant improvement of renal function might be observed among patients of CTEPH with CKD.

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 combined BPA therapy improves pulmonary and systemic hemodynamics, with positive effects on renal function, which maybe an alternative treatment option for improving clinical

outcomes.

## Declarations

### Ethics approval and consent to participate

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. was approved by the Research Ethics Committee of the Second Affiliated Hospital of Harbin Medical University, China. Informed consent was obtained from each patient.

### Consent for publication

Not applicable.

### Availability of data and materials

All data can be obtained from the manuscript or from request to the author.

### Competing interests

The authors declare no conflict of interest.

### Funding

None.

### Author contributions

Research idea and study design: YZ and XYW; data acquisition: YZ, YXZ, CL, and XYW; data management: YZ; statistical analysis: CL; interpretation: YZ and XYW; supervision or mentorship: CL and XYW; organization of the study: YZ, YXZ, CL, and XYW. All authors approved the final version.

### Acknowledgements

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## Tables

**Table 1.** Baseline characteristics

	rhBNP group (n=26)	Control group (n=21)	P-value
Age at first BPA, years	67.04±7.47	63.24±10.07	0.145
Men, n (%)	13 (50.00)	12 (57.14)	0.770
BMI, kg/m <sup>2</sup>	24.08±2.84	24.29±1.98	0.777
6MWD, m	377.38±18.95	376.90±23.08	0.938
<b>Vital signs</b>			
Systolic blood pressure, mmHg	109.04±11.70	106.10±14.63	0.447
Heart rate, beats/min	94.19±5.10	95.33±4.89	0.441
Respiratory rate, breaths/min	22.15±3.55	22.52±5.62	0.795
<b>Serum values</b>			
WBC, ×10 <sup>9</sup> /L	12.89±5.06	14.70±3.55	0.174
CRP, mg/L	8.82±4.09	8.97±3.20	0.886
D-dimers, µg/L	191.31±85.15	153.10±56.29	0.084
NT-proBNP, pg/mL	1152.00±250.02	1091.38±331.25	0.478
Troponin I, µg/L	0.77±0.49	0.84±0.54	0.648
Serum sodium, mmol/L	142.22±2.60	142.21±0.35	0.993
<b>Echocardiographic parameters</b>			
RV diameter, mm	37.98±7.08	39.57±7.80	0.468
RV hypokinesis, n (%)	10 (38.46)	9 (42.86)	0.775
RVSP, mmHg	51.27±9.00	49.14±7.98	0.402
TAPSE, cm	2.12±1.11	1.91±0.55	0.418

Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. BPA, balloon pulmonary angioplasty; BMI, body mass index; 6MWD, six-minute walk distance; WBC, 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; RVSP, right ventricular systolic pressure.

**Table 2.** Invasive hemodynamic measurements in patients with the first right cardiac catheterization

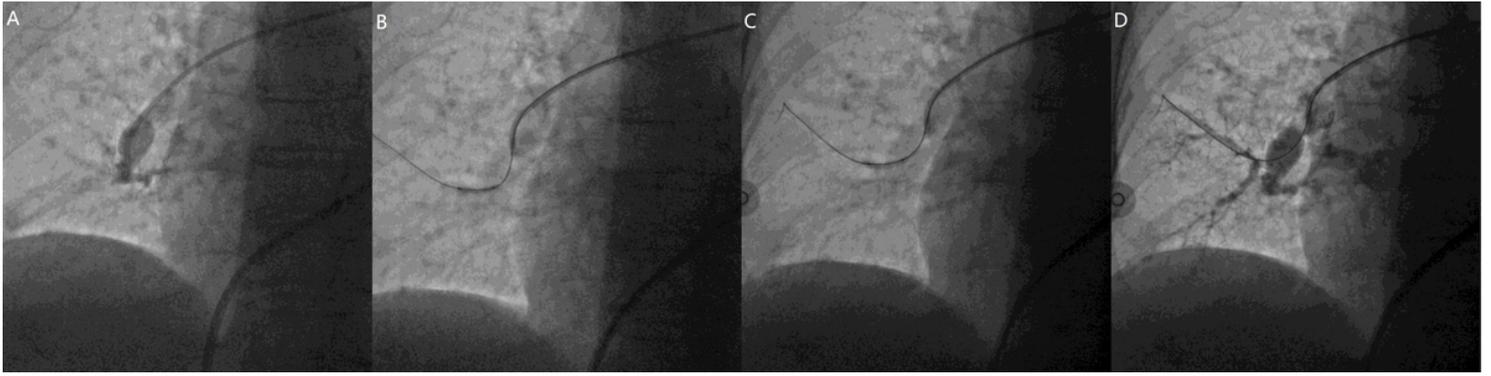
	rhBNP group (n=26)	Control group (n=21)	<i>P</i> -value
Pulmonary artery systolic pressure, mmHg	41.58±19.51	39.95±10.25	0.716
Pulmonary artery diastolic pressure, mmHg	17.19±10.45	17.33±7.19	0.958
Pulmonary artery mean pressure, mmHg	25.04±12.16	24.24±3.93	0.754
Right atrial mean pressure, mmHg	5.62±4.71	5.62±2.92	0.997
Right ventricular mean pressure, mmHg	17.50±9.65	16.86±3.81	0.758
Pulmonary arterial oxygen saturation, %	64.46±12.11	64.52±4.41	0.981
Cardiac output, L/min	5.22±1.40	5.26±1.26	0.923
Cardiac index, L/min per m <sup>2</sup>	2.87±0.80	2.52±0.81	0.141
Pulmonary vascular resistance, wood	3.03±2.39	3.33±1.82	0.636

**Table 3.** Characteristics in 6-month follow-up after the last BPA

	rhBNP group (n=26)	Control group (n=21)	<i>P</i> -value
6MWD, m	415.92±14.63	408.69±10.47	0.132
<b>Vital signs</b>			
Systolic blood pressure, mmHg	109.08±14.65	105.50±15.03	0.525
Heart rate, beats/min	85.46±3.53	85.25±7.96	0.925
Respiratory rate, breaths/min	19.08±1.80	18.38±5.12	0.615
<b>Serum values</b>			
WBC, ×10 <sup>9</sup> /L	9.60±2.20	10.53±3.98	0.458
CRP, mg/L	5.42±3.02	7.19±2.74	0.111
D-dimers, µg/L	164.62±57.75	152.81±46.46	0.547
NT-proBNP, pg/mL	387.31±105.87	519.94±221.31	0.046
Troponin I, µg/L	0.26±0.19	0.89±0.29	<0.001
Serum sodium, mmol/L	144.98±2.76	144.64±3.67	0.780
<b>Echocardiographic parameters</b>			
RV diameter, mm	34.78±4.79	41.51±11.14	0.041
RV hypokinesis, n (%)	13 (50.00)	16 (76.19)	0.80
RVSP, mmHg	39.62±6.81	42.31±6.31	0.279
TAPSE, cm	3.76±0.52	3.30±0.66	0.045

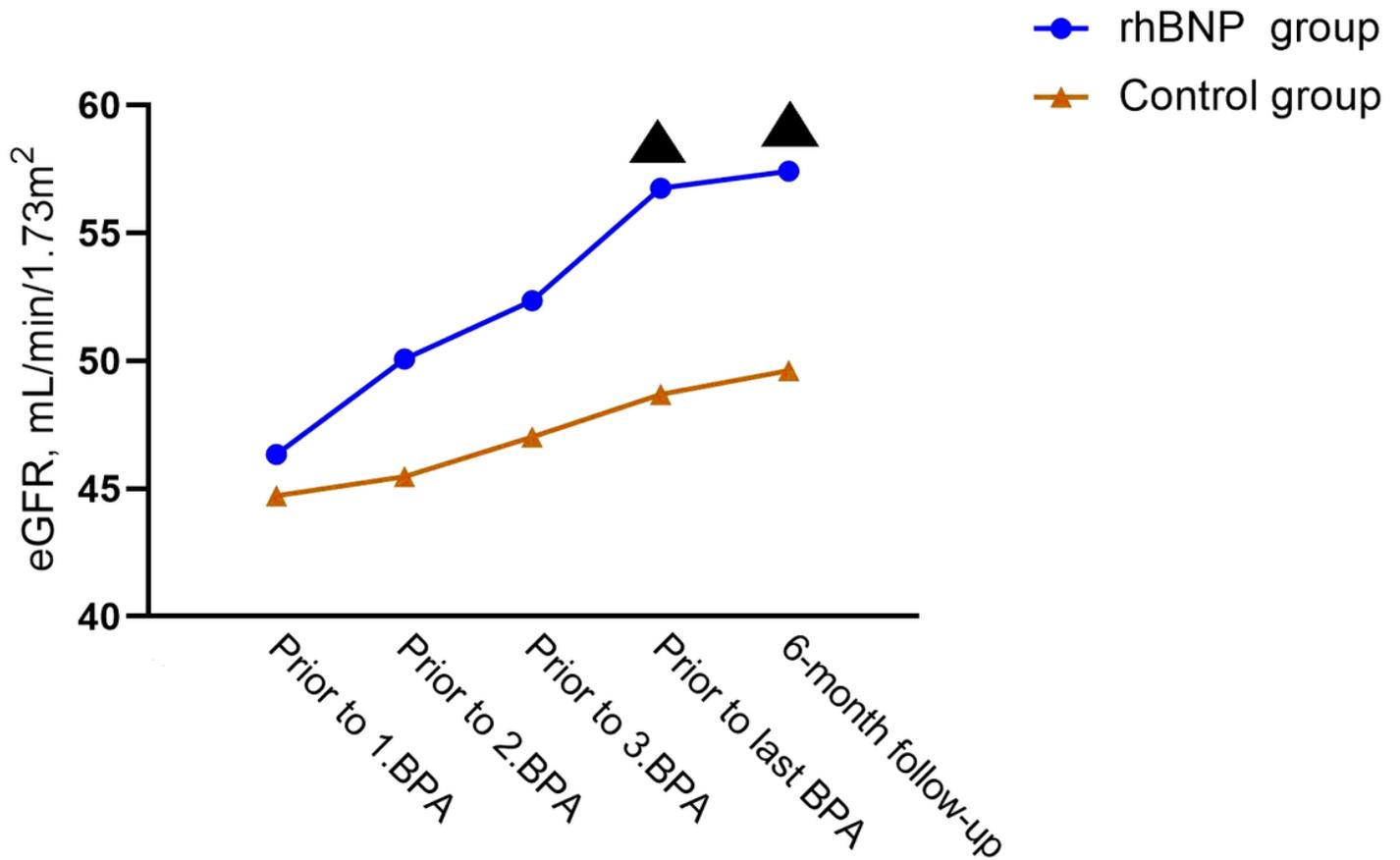
Mean values (standard deviation) and % (n) were reported for continuous and categorical variables, respectively. BPA, balloon pulmonary angioplasty; 6MWD, six-minute walk distance; WBC, white blood cell; CRP, C-reactive protein; NT-proBNP, N-terminal pro-B type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricle; RVSP, right ventricular systolic pressure.

## Figures



**Figure 1**

Digital subtraction angiography of the middle lobe arteries in a 73-year-old woman with inoperable chronic thromboembolic pulmonary hypertension (CTEPH) showing balloon pulmonary angioplasty (BPA). (A) Pulmonary arteriography before BPA. (B-C) BPA. (C) Pulmonary arteriography after BPA.



**Figure 2**

Dynamics of renal functional parameters during BPA therapy (laboratory analysis prior to the BPA procedure). eGFR, estimated glomerular filtration rate; BPA, balloon pulmonary angioplasty.

▲Significance between rhBNP group and control group.

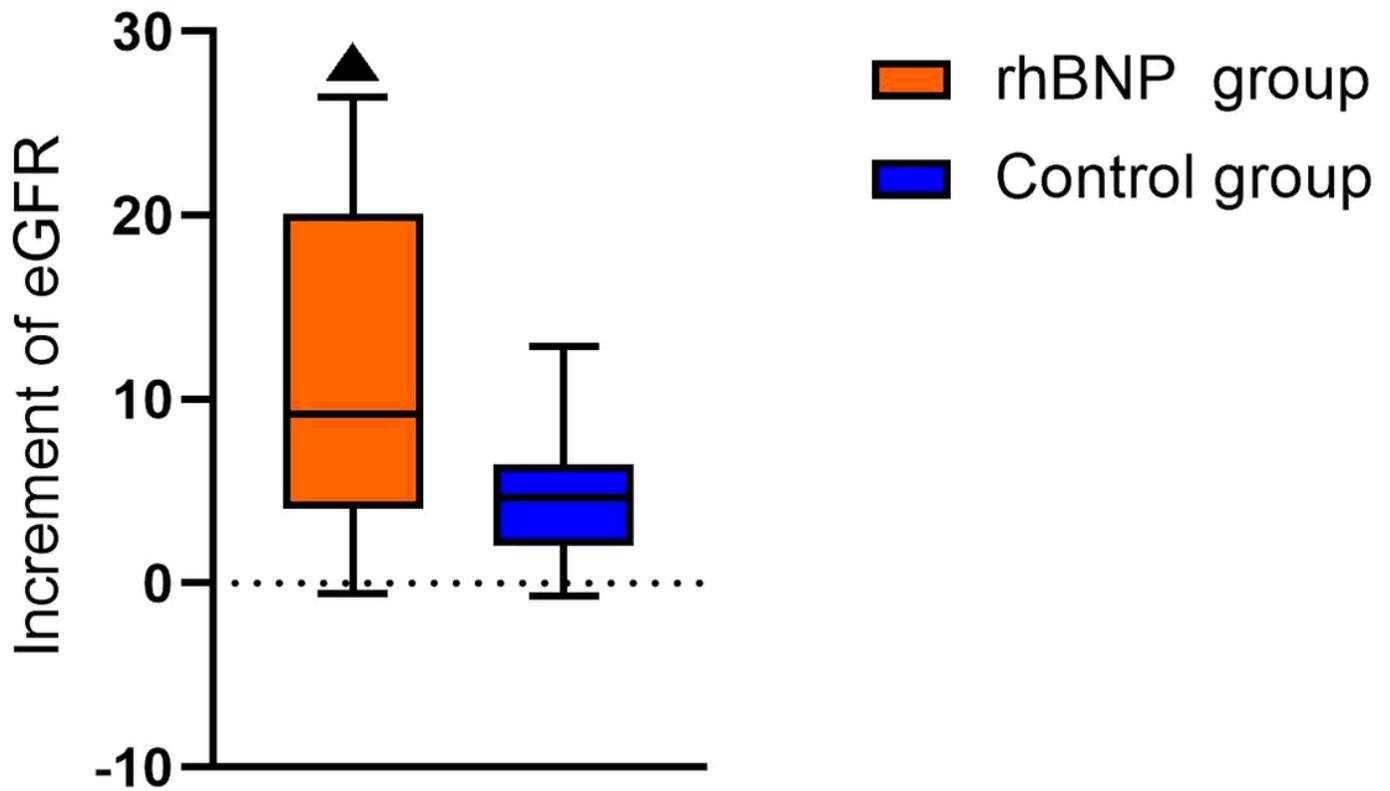


Figure 3

The average increment of eGFR from baseline to follow-up. eGFR, estimated glomerular filtration rate.

▲Significance between rhBNP group and control group.

## Supplementary Files

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