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Benefits of recombinant human brain natriuretic peptide to improve ventricular function and hemodynamics in patients with ST-elevation myocardial infarction.

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Keywords: ST-segment elevation myocardial infarction; recombinant human brain natriuretic peptide; tirofiban; primary percutaneous coronary intervention.

Abstract. This study aimed to assess the impact of recombinant human brain natriuretic peptide (rh-BNP) on ventricular function and hemodynamics in post-ST-segment elevation myocardial infarction (STEMI). We compared the outcomes of 65 STEMI patients treated with rh-BNP to an equal cohort given tirofiban following percutaneous coronary intervention (PCI). Data collected pre- and post-intervention included biochemical markers, TIMI (Thrombolysis In Myocardial Infarction) grade, hemodynamics, thrombotic score (TS), left ventricular ejection fraction (LVEF), high-sensitivity C-reactive protein (CRP) levels, liver and kidney function, and ECG. The TIMI level ($p=0.03$), the ratio of TIMI myocardial perfusion grade III ($p=0.04$), and the thrombus score ($p<0.001$) in the rh-BNP group after the intervention markedly exceeded those in the tirofiban group. After correction, the TIMI frame count (CTFC) ($p=0.02$), the incidence of slow flow ($p=0.02$), thrombus score ($p<0.001$), stent length ($p=0.02$) as well as times of administration of sodium nitroprusside medication in the rh-BNP group were markedly below those in the tirofiban group ($p=0.01$). Creatine kinase (CK) ($p<0.001$), CK-MB ($p=0.01$), and N-terminal pro-b-type natriuretic peptide (NT-proBNP) ($p<0.02$) in the rh-BNP group were markedly below those the in tirofiban group 24 hours after intervention; and the sum-STR ($p<0.03$) immediately after intervention markedly exceeded that in the tirofiban group. No significant differences were found in major cardiac adverse events (MACE) between the treatments. At the 30-day follow-up, rh-BNP showed a more effective enhancement of blood flow status, with the safety profiles of both treatments being comparable. The findings suggest that the rh-BNP has significant potential for treating PPCI-related slow flow.

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Beneficios del péptido natriurético cerebral humano recombinante para mejorar la función ventricular y la hemodinámica en pacientes con infarto de miocardio con elevación del segmento ST.

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Palabras clave: infarto de miocardio con elevación del segmento ST; péptido natriurético recombinante del cerebro humano; tirofibán; intervención coronaria percutánea primaria.

Resumen. El objetivo de este estudio fue evaluar el impacto del péptido natriurético cerebral humano recombinante (rh-BNP) sobre la función ventricular y la hemodinámica después de un infarto de miocardio con elevación del segmento ST (STEMI). Comparamos los resultados de 65 pacientes con STEMI tratados con rh-BNP con un grupo equivalente tratado con tirofiban tras la intervención coronaria percutánea (PCI). Los datos recopilados antes y después de la intervención incluyeron marcadores bioquímicos, grado TIMI (Trombolisis en infarto del miocardio), hemodinámica, puntuación trombótica (TS), fracción de eyección del ventrículo izquierdo (LVEF), niveles de proteína C reactiva de alta sensibilidad (CRP), función hepática y renal y ECG. El nivel de TIMI (p=0,03), la proporción de grado de perfusión miocárdica TIMI III (p=0,04) y la puntuación trombótica (p<0,001) en el grupo rh-BNP después de la intervención superaron significativamente a aquellos en el grupo de tirofiban. Tras la corrección, el conteo de fotogramas TIMI (CTFC) (p=0,02), la incidencia de flujo lento (p=0,02), la puntuación trombótica (p<0,001), la longitud del stent (p=0,02) así como las veces de administración de la medicación de nitroprusiato de sodio en el grupo rh-BNP fueron notablemente inferiores a los del grupo de tirofiban (p=0,01). La CK (p<0,001), la CK-MB (p=0,01) y la NT-proBNP (p<0,02) en el grupo rh-BNP fueron significativamente inferiores a los del grupo de tirofiban 24 horas después de la intervención, y la sum- ST-segment resolution (STR) (p<0,03), inmediatamente después de la intervención superó significativamente a la del grupo de tirofiban. No se encontraron diferencias significativas en los eventos adversos cardiacos mayores (MACE) entre los tratamientos. En el seguimiento de 30 días, el rh-BNP mostró una mejora más efectiva del estado del flujo sanguíneo, siendo los perfiles de seguridad de ambos tratamientos comparables. Los hallazgos sugieren que el rh-BNP tiene un potencial significativo para tratar el flujo lento relacionado con PPCI.

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INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a severe form of heart attack characterized by a prolonged period of blocked blood supply that affects a large area of the heart muscle [1]. The mean age of a first MI is 65.1 for men, while for women, it is 72. An ST-elevation myocardial infarction affects around 38% of patients with acute coronary syndrome when they arrive at the hospital [2].

STEMI is commonly caused by the rupture of an atherosclerotic plaque in a coronary artery, leading to the formation of a blood clot that completely blocks the artery and interrupts blood flow to the heart muscle. This results in myocardial ischemia and, if not promptly treated, irreversible damage to the heart muscle [1,2].

The symptoms of STEMI can include chest pain or discomfort, shortness of breath, nausea, lightheadedness, and pain or discomfort in other areas of the upper body, such as the arms, back, neck, jaw, or stomach [3].

Diagnosis of STEMI is primarily based on the clinical presentation, ECG findings, and the elevation of cardiac biomarkers. An ECG demonstrating ST-segment elevation is considered diagnostic, particularly when complemented by symptoms indicative of ischemia. Furthermore, cardiac enzymes such as troponins are utilized to confirm myocardial damage [1,4].

Treatment of STEMI focuses on the timely restoration of coronary blood flow, typically achieved through reperfusion therapies such as percutaneous coronary intervention (PCI) or thrombolytic therapy [5]. Adjuvant therapies include antiplatelet agents, anticoagulants, beta-blockers, and angiotensin-converting enzyme inhibitors to reduce myocardial oxygen demand and prevent further thrombus formation [6,7].

In this context, recombinant human brain natriuretic peptide (rhBNP) therapy emerges as a novel adjunct in managing STEMI. rhBNP, a synthetic form of the naturally occurring brain natriuretic peptide, has shown promise in improving ventricular function and hemodynamics [8]. Its mechanisms of action include vasodilation, natriuresis, and the inhibition of the renin-angiotensin-aldosterone system, which collectively contribute to reduced cardiac load and improved myocardial recovery [9]. According to a study by Zhou *et al.* [10], rhBNP has shown promise in improving ventricular function and hemodynamics in patients with end-stage renal disease and type 4 cardiorenal syndrome. Another study by Liang *et al.* suggests that rhBNP combined with catheter-directed therapy may improve right ventricular dysfunction and stabilize hemodynamics in patients with acute pulmonary embolism [11].

Given the high stakes of STEMI management and the potential impact on patient outcomes, a comprehensive evaluation of rhBNP's efficacy and safety is warranted. Since limited studies have been conducted in this field, especially in the Middle East, this study was essential to elucidate the effect of the therapeutic effect of recombinant human brain natriuretic peptide in patients with myocardial infarction by increasing the ST piece.

MATERIALS AND METHODS

General information

The research is a retrospective study using case data. The criteria for selecting patients in this study were as follows: the diagnosis of STEMI symptoms following views of the "STEMI Diagnosis and Treatment Guidelines" [6]; patients received PCI treatment within 12 h after admission; treatment with tirofiban (TIF) or rh-BNP after PCI; no allergic reactions were observed after treatment with TIF or rh-BNP; did not receive intravenous thrombolysis treatment before PCI; Killip level exceeds that of Grade III or cardiogenic shock patients. Exclusion criteria: patients with comorbidities of organ and tissue diseases such as brain, heart, kidney, and liver; patients with severe aortic stenosis; patients with mental or other cognitive impairments or who refuse to cooperate with the experiment; patients with pulmonary hypertension caused by pulmonary heart disease or other reasons; patients with a history of MI, valvular heart disease, dilated cardiomyopathy, HF, hypertrophic cardiomyopathy, or other general diseases. Given the above standards, this study collected the medical history information of 142 STEMI patients

admitted to our hospital from June 2021 to June 2023, with 130 participants included in the experimental study. In the queue, 65 patients received treatments with TIF, while the remaining cases received treatments with rh-BNP. All sufferers had clinical and pathological features taken and signed an informed consent form to use this information. This research was approved by the Ethics Committee of the Medical Center to collect relevant information from sufferers (approval number: MEC-2021-06). All work was carried out following the provisions of the Declaration of Helsinki. The research process is demonstrated in Fig. 1.

Treatment strategies

All patients took 300 mg aspirin orally, clopidogrel 300 mg/ticagrelor 180 mg, and intravenous heparin 5000 IU at admission. Coronary artery angiography (CAG) was carried out before intervention to determine the quantity of the pathological branches, for patients who received treatments with rh-BNP, 5 mg of medication was injected intravascularly during the intervention period, followed by implantation of a stent and re-administration of 5 mg of rh-BNP. If the symptoms of slow BF persisted, they were given a last 5 mg dose of rh-BNP. Sufferers who received treatments with TIF were slowly injected 5 mg/kg through the CA during the intervention period. After the stent implantation, 5 mg/kg TIF was administered via CA again. 3 mg/kg TIF was injected through the CA for sufferers with slow BF symptoms. After 24 hours of intervention, all patients were given aspirin 100 mg, clopidogrel 75 mg/ticagrelor 90 mg and heparin 5000 IU for 5-7 days. Patients were followed up for 30 days after discharge, and MACE (Major Adverse Cardiovascular Events) were recorded.

Measurement of treating outcomes

The myocardial infarction thrombolysis (TMI) classification, hemodynamic parameters, thrombotic score (TS) [7], left ventricular ejection fraction (LVEF), CRP level, uric acid, liver and kidney functions, electrocardiogram (ECG), echocardiography and other information of patients before and after the intervention were collected to compare differences in the therapeutic effects (treatment efficacy) and SE of the two treatment methods.

Statistical analysis

Relevant analysis was conducted using the SPSS version 19.0 software (IBM®,

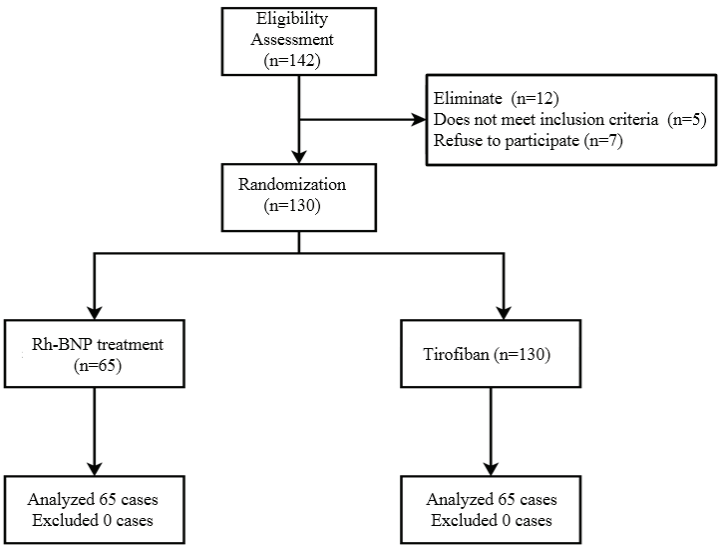

Fig. 1. Research Process.

Armonk, NY). Continuous data was denoted by mean ± standard deviation (SD). The number of cases denotes classified data. The Student test was used to compare the differences between consecutive data sets. Chi-square and Fisher's exact tests were used to determine whether there are differences between different categories of index groups. $p<0.05$ is statistically significant.

RESULTS

Patient baseline characteristics

The analysis of baseline data among the sufferers participating in this experiment did not demonstrate significant differences (SD) in preoperative age, body mass index (BMI), and other indicators. Table 1 demonstrates the details.

No statistically significant differences were among the sufferers participating in this experiment in combined medication (Table 2).

Intervention Information

Table 3 indicates no differences in the number of branches, number of stents, and score of thrombus before the intervention, systolic blood pressure, and other relevant respects. However, after the intervention, the TMI changes in thrombus score levels in the rh-BNP group and other relevant aspects dramatically exceeded those in the TIF group (Table 3). On the other hand, the TMI Frame Count (CTFC), slow flow (SF) incidence, post-intervention thrombus score, stent length, and sodium nitroprusside administration times after correction were dramatically ´lower in the TIFgroup (Table 3).

The effect of rh-BNP or TIF on the treating outcomes of PCI

Twenty-four hours after PCI intervention, creatine kinase (CK), creatine kinase isozyme (CKMB), and the amino-terminal fraction of B-type natriuretic peptide (NT pro-BNP) in the rh BNP group were dramati-

Table 1
Baseline Characteristics.

Characteristic	rh-BNP(n=65)	TIF(n=65)	t/χ^2	*p*
Age (years)	60.19±10.02	58.96±10.14	1.462	0.09
Gender (male, %)	47(72.3)	51(78.5)	-0.613	0.36
BMI(kg/m^2)	25.94±3.54	25.44±3.29	0.837	0.50
Time before balloon dilation(min)	227.98±68.52	232.19±86.43	-0.388	0.63
Killip classification				
Level 1 (n, %)	61(93.8)	60(92.3)	0.117	0.69
Level 2 (n, %)	4(6.2)	5(7.7)		
Smoke (n,%)	41(63.1)	40(61.5)	0.035	0.85
Drink (n,%)	24(36.9)	14(21.5)	3.710	0.06
Hypertension (n, %)	41(63.1)	47(72.3)	1.258	0.27
Level 1 (n, %)	8(12.3)	7(10.8)		
Level 2 (n, %)	16(24.6)	14(21.5)	0.286	0.85
Level 3 (n, %)	17(26.2)	19(29.2)		
Diabetes (n, %)	18(27.7)	21(32.3)	0.328	0.56
Cerebral Infarction (n, %)	8(12.3)	11(16.9)	0.525	0.49

t: t-test; χ^2: Chi-squared test; BMI: body mass index; rh-BNP: B-type recombinant human brain peptide.
TIF: tirofiban.

Table 2
Information on drug combination use.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p* value
Ticagrelor (n, %)	59(90.8)	61(93.8)	-	0.39
Statins (n, %)	62(95.4)	61(93.8)	-	0.53
Nitrates (n, %)	45(69.2)	48(73.8)	0.443	0.44
β-blocker (n, %)	57(87.7)	52(80.0)	1.690	0.13
ACEI/ARB	52(80.0)	56(86.2)	1.259	0.29
CCB (n, %)	21(32.3)	22(33.8)	0.884	0.36
PPI (n, %)	48(73.8)	52(80.0)	0.705	0.44
Hypoglycemic drugs (n, %)	21(32.3)	23(35.4)	0.327	0.53

t: t-test, χ^2: Chi-squared test; rh-BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; ACEI: ACE inhibitor; ARB: angiotensin II receptor antagonist; CCB: calcium channel blocker (calcium antagonist); PPI: proton pump inhibitor.

cally lower than in the TIF group. The LEVF changes in the rh-BNP group (RBG) dramatically exceeded those in the TIF group. (Table 4).

However, there were no statistical differences among the sufferers participating in this experiment in CK (p=0.13) and CKMB (p=0.18) at the peak recording time points. The sum STR in the RBG also markedly exceeded that in the TIF group immediately after intervention (Table 5), and there were no differences in sum STR two hours after the intervention (Table 5).

Major Adverse Cardiovascular Events (MACE)

The incidence of angina and HF in the RBG was dramatically lower than in the TIF group (Table 6). On the other hand, in terms of CA occlusion microbleeds, the incidence of TMI microbleeds, the overall utilization of streptokinase, tissue type plasmin activator, and other relevant aspects in the RBG markedly exceeded those in the TIF group (Table 6). Both groups of patients did not experience MI or other severe side effects (Table 6).

Discharge follow-up

After discharge, there was no follow-up loss for 30 days. According to the information shown in Table 7, there were no differences in physiological indicators and MACE among the patients participating in this experiment (Table 7).

DISCUSSION

PCI can markedly unblock the infarcted CA and was chosen as the first-line treatment strategy for STEMI clinical treatment. Recent studies given a large sample suggest that PCI can construct BF in >90% of IRA and restore TMI to level 3 [12]. However, the effect of PCI is offset by some severe side effects. Slow/no BF is a risk element influencing the prognosis of SEMI patients. Some drugs were utilized to enhance the therapeutic effect of PCI to enhance coronary BF after PCI.

Compared to studies with TIF, few people have focused on the influence of rh-BNP on coronary BF after PCI. Guo *et al.* showed that compared to patients treated with PCI alone, rh-BNP can significantly reduce the incidence of slow BF, indicating the potential of rh-BNP to improve BF after PCI [13]. Therefore, this study compared the therapeutic influences of rh-BNP and TIF on PCI-related slow/no flow. The outcomes demonstrated that compared with TIF, administering rh-BNP markedly reduced the occurrence of SF after PCI.

Table 3
Information on treatment outcomes for patients with myocardial infarction with elevation of the segment ST (STEMI) and percutaneous coronary intervention (PCI) patients.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p* value
Number of branches				
Single branch (n,%)	8(12.3)	7(10.8)		
Double branches (n,%)	19(29.2)	17(26.2)		
Three branches (n,%)	38(58.5)	41(63.1)	0.286	0.87
IRA distribution				
LAD (n,%)	33 (50.8)	38(58.5)		
LCX (n,%)	10 (15.4)	7(10.8)		
RCA (n,%)	22 (33.8)	20(30.8)	0.977	0.61
TMI level before PCI				
Level 0 (n,%)	19(29.2)	25(38.5)	2.298	0.51
Level 1 (n,%)	8(12.3)	8(12.3)		
Level 2 (n,%)	9(13.8)	11(16.9)		
Level 3 (n,%)	29(44.6)	21(32.3)		
TMI level after PCI				
Level 0 (n,%)	1(1.5)	2(2.3)	-	0.03
Level 1 (n,%)	2(3.1)	7(6.9)		
Level 2 (n,%)	6(9.2)	11(13.1)		
Level 3 (n,%)	56(86.2)	45(77.7)		
CTFC after PCI (FPS)	23.60±4.05	25.57±5.29	-2.381	0.02
Level 3 TMPG after PCI (n,%)	58(89.2)	49(75.5)	4.279	0.04
TS score before PCI	3(2,4)	3(2,4)	-1.45	0.15
TS score after PCI	0(0,1)	1(0,1)	-3.908	<0.001
TS score changes	3(2,3)	1(1,1)	-4.263	<0.001
Support number	1(1,1)	1(1,2)	-0.898	0.37
Support length(mm)	26.4±11.33	31.35±12.93	-2.323	0.02
Thrombotic aspiration during intervention (n,%)	15(23.1)	14(21.5)	0.044	0.83
Intraoperative hypotension (n,%)	5(7.7)	7(10.8)	0.367	0.55
Intraoperative systolic blood pressure (mmHg)	125.58±18.87	122.88±21.06	0.772	0.44
Intraoperative diastolic blood pressure (mmHg)	70.66±5.09	70.69±11.50	-0.2	0.98
HR (n/min)	72.23±8.46	72.58±7.65	-0.25	0.80
SF/no flow (n,%)	9(13.8)	20(30.8)	5.370	0.02
Use of sodium nitroprusside (n,%)	4(6.2)	15(23.1)	-	0.01

t: t-test, $\chi 2$: Chi-squared test; rh-BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; CTFC: corrected TMI frame count; FPS: frames per second; IRA: infarction-related artery; LAD: anterior descending branch of left CA; LCX: left circumflex branch; PCI: primary PCI; RCA: right CA; rh-BNP: B-type recombinant human brain natriuretic peptide; TMI: thrombolysis for MI; TMPG: TMI myocardial perfusion level; TS: thrombotic score; HR: heart rate; SF: slow flow.

Table 4
Effects of two treating methods on ventricular function and ejection fraction.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p*
CK peak (U/L)	2108±1452	3562±1609	0.260	0.13
CKMB peak (U/L)	168.4±112.3	206.9±139.2	0.117	0.18
Ln (NT-proBNP)	5.96±0.75	7.43±0.93	0.122	0.15
LEVF	48.32±9.86	52.08±10.04	0.103	0.42

t: t-test, χ^2: Chi-squared test; rh-BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; CK: creatine kinase; CKMB: creatine kinase isozyme; NT-proBNP: N-terminal pro B-type natriuretic peptide.

Table 5
The impact of two treatment methods on the total STR at two hours after PCI surgery.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p*
Total STR after PCI surgery				
<30% (n,%)	5(7.7)	12(18.5)		
30%-70% (n,%)	13(21.5)	21(32.3)		
>70% (n,%)	47(70.8)	32(49.2)	6.795	0.03
Total STR at two hours after PCI surgery				
<30% (n,%)	3(4.6)	8(12.3)		
30%-70% (n,%)	9(13.8)	12(18.5)		
>70% (n,%)	53(81.5)	45(69.2)	3.408	0.17

t: t-test, χ^2: Chi-squared test; Rh BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; PCI: primary PCI; STR: ST-segment resolution.

Table 6
The impact of two treatment methods on the total STR at two hours after PCI surgery.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p*
Heart failure (n, %)	11(16.9)	23(35.4)	5.735	0.03
Mortality (n, %)	1(1.5)	0(0)	-	0.32
Angina pectoris (n, %)	8(12.3)	18(27.7)	4.808	0.03
TMI level				
Microbleeds (n, %)	17(26.2)	8(12.3)	4.011	0.04
GUSTO				
pyorrhea (n, %)	17(26.2)	8(12.3)	4.011	0.05

t: t-test, χ^2: Chi-squared test; PCI: primary PCI; STR: ST-segment resolution: rh-BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; TMI: thrombolysis myocardial infarction; GUSTO: the application of streptokinase and tissue type plasmin activator in the treatment of coronary occlusion.

In addition, the thrombus score of patients receiving treatments with rh-BNP was evidently lower than that of TIF. It may be due to the more substantial thrombolytic function of rh-BNP on existing thrombi in the CA[14]. Regarding biochemical parameters, the two clinically recognized myocardial function indicators, CK and CKMB, showed significantly lower peak levels in the RBG compared to the TIF group.

Table 7
The impact of two treatment methods on the total STR at two hours after PCI surgery.

Characteristic	rh-BNP (n=65)	TIF (n=65)	t/χ^2	*p*
CK (U/L)	82.50±27.29	80.66±29.18	0.369	0.71
CKMB (U/L)	12.58±6.76	12.63±6.91	0.046	0.95
HSCRP (mg/L)	2.18±1.09	2.52±1.61	1.381	0.16
Ln (NT-proBNP)	5.23±0.85	5.41±1.22	0.941	0.34
LVEF (%)	17(26.2)	8 (12.3)	4.011	0.04
Mortality	0	0	-	-
Secondary MI	0	0	-	-
Treatment Failure	5(7.8)	9(13.8)	1.209	0.26
Angina pectoris	7(10.9)	5(9.3)	0.427	0.55

t: t-test, χ^2: Chi-squared test; PCI: primary PCI; STR: ST-segment resolution. rh-BNP: B-type recombinant human brain natriuretic peptide; TIF: tirofiban; CK: creatine kinase; CK-MB: creatine kinase-myocardial band; NT-proBNP: N-terminal pro b-type natriuretic peptide; LVEF: left ventricular ejection fraction.

At the same time, side effects were absent among the sufferers participating in this experiment at the peak time point [15]. In addition, the NT pro-BNP, which serves as a marker for the degree of myocardial injury, was also lower in the RBG than in the TIF group [16]. These data clearly indicate that rh-BNP has a more substantial protective effect on PCI treatment-related injuries than TIF.

The electrocardiogram examination of the patient's myocardial function revealed that the sum-STR changes in the RBG were superior to those in the TIF group. Previous studies demonstrated a positive correlation between the recovery of myocardial ischemic injury and the recovery of sum-STR [17]. Integrated with the significant changes in LVEF in the RBG, it can be seen that the improvement in the influence of rh-BNP on myocardial function is also more marked than that of TIF. In addition, the incidence of MACE in the RBG was below that in the TIF group, representing rh-BNP's safety in clinical application. This study followed all patients for 30 days after discharge, and the results showed no differences in biochemical, myocardial function, MACE, and other parameters between the two groups of patients, further proving the potential of rh-BNP in improving CA BF after PCI surgery. Existing research also indicates that the influence of rh-BNP on the heart is more pronounced after intervening, but over time, the disparity in treating efficacy in the two drugs decreases. This decrease may be because of the more substantial function of rh-BNP in enhancing microcirculation by dissolving small blood clots [14].

In conclusion, the current research compared the effectiveness of rh-BNP and TIF in preserving STEMI patients from PCI-related ischemia/reperfusion (I/R) injury. The results show that both drugs significantly reduce the occurrence of SF and MCAE and improve myocardial function. Additionally, during the 30-day follow-up, rh-BNP had a more substantial immediate effect on most indicators after the intervention than TIF. The safety of its application was similar, suggesting good potential for clinical use in treating PCI-related SF.

Notably, the study has various limitations. Firstly, it is a retrospective study using case data, potentially introducing bias and limiting the findings' generalizability. Secondly, the sample size is relatively small. Thirdly, the study lacks information on the long-term outcomes of the two treatment

methods, which is crucial for understanding their overall effectiveness and safety.

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There are no conflicting interests

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Authors contribution

DS, XL: Designed the study work and performed the experiments. LY, CL: Analyzed the data and wrote the manuscript. JM: Drafted and edited the manuscript.

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