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Intracoronary Nicorandil and the Prevention of the No-Reflow Phenomenon During Primary Percutaneous Coronary Intervention in Patients with Acute ST-Segment Elevation Myocardial Infarction

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Statistical Analysis C
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Background: This study aimed to investigate intracoronary nicorandil treatment on the no-reflow phenomenon (NRP) during primary percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) and to compare nicorandil with sodium nitroprusside.

Material/Methods: Patients with sustained acute STEMI who underwent primary PCI (N=120) were randomly assigned to three groups: the nicorandil-treated group (N=40) had 2 mg of nicorandil injected into the coronary artery at 2 mm beyond the occlusion with balloon pre-dilation; the sodium nitroprusside-treated group (N=40) underwent the same procedure, but with 200 μg of sodium nitroprusside; the control group (N=40) received PCI and balloon pre-dilation only. Coronary angiography, incidence of NRP, hypotensive episodes, ST-segment resolution (STR) rate, levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), wall motion score index (WMSI), and left ventricular ejection fraction (LVEF) were measured before and after primary PCI. Major adverse cardiovascular events (MACEs) post-PCI and at three-month follow-up were recorded.

Results: Patients in the sodium nitroprusside and nicorandil groups had significantly improved thrombolysis in myocardial infarction (TIMI) scores, TIMI myocardial perfusion grade (TMPG), and ST-segment elevation resolution (STR) ($P<0.05$), and a significantly lower incidence of NRP ($P=0.013$). The incidence of intraoperative hypotension in the sodium nitroprusside group was significantly greater than the nicorandil and control groups ($P=0.035$).

Conclusions: Patients with sustained acute STEMI undergoing primary PCI, treated with intracoronary nicorandil had a reduced incidence of the NRP, improved myocardial perfusion and cardiac function.

MeSH Keywords: Coronary Vessels • Myocardial Infarction • Nicorandil • No-Reflow Phenomenon

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Background

Primary percutaneous coronary intervention (PCI) is one of the most effective treatments for acute ST-segment elevation myocardial infarction (STEMI) [1,2]. The no-reflow phenomenon (NRP) is the inadequate reperfusion of the myocardium of a given coronary artery segment in the absence of angiographic evidence of obstruction of the coronary artery [3]. The NRP has a reported prevalence of >30% in patients with acute STEMI who undergo primary PCI and can lead to an adverse clinical outcome, including arrhythmia, heart failure, sudden cardiac death, and other major cardiovascular complications [4,5]. Although there have been several reports on the pathogenesis of the NRP, there have been few studies on the effective prevention and treatment of the NRP.

Nicorandil an ATP-sensitive potassium (KATP) opener, with nitrate-like characteristics that result in coronary artery dilatation, increase in coronary artery blood flow, ischemic preconditioning, anti-arrhythmic effects, and reduction of ischemic reperfusion injury [6,7]. Although the use of nicorandil in the treatment of the NRP occurring after PCI has been previously reported, the intracoronary use of nicorandil for the prevention of the NRP following primary PCI has not been previously reported [4].

The aim of this study was to investigate the effect of intracoronary nicorandil on the NRP during primary PCI in patients with acute STEMI and to compare nicorandil with sodium nitroprusside.

Material and Methods

Patients studied

From January 2013 to December 2016, in the Third Hospital of Hebei Medical University, 120 patients were diagnosed with acute ST-segment elevation myocardial infarction (STEMI) who also received primary percutaneous coronary intervention (PCI) and were included in the study.

Acute STEMI was defined according to the World Health Organization (WHO) definition, and included: ischemic chest pain lasting ≥20 minutes, radiating to the left upper arm, lower jaw, neck, back or shoulder that could not be relieved by oral nitrates; changes of myocardial infarction (MI) on the electrocardiogram (ECG): new significant ST-segment elevation ≥1 mV, in more than two standard leads, or ≥2 mV in more than two contiguous precordial leads, or new left bundle branch block (LBBB), with or without pathological Q waves; an increase in the levels of serum cardiac enzyme, such as cardiac troponin I (cTnI) and creatine kinase isoenzyme MB (CK-MB) [8]. Any two of these characteristics were consistent with the WHO diagnosis of STEMI [8]. All patients underwent primary PCI within 12 hours of the onset of acute STEMI. A requirement for all patients was a blood pressure measurement greater than 90/60 mmHg before primary PCI was performed.

The exclusion criteria for patients in this study included: the presence of cardiogenic shock (Killip class IV); severe hypertension (blood pressure ≥180/110 mmHg) without control; severe multiple organ failure; a recent history of coronary artery bypass graft (CABG); a clinical diagnosis of aortic dissection; patients who were not physically able to tolerate PCI.

This study was approved by the local Ethics Committee of the Hebei Medical University. All patients who participated in the study signed an informed consent, or their authorized persons signed an informed consent.

Patient treatment groups

Patients with sustained acute STEMI who underwent primary PCI (N=120) were randomly assigned to three groups: the nicorandil-treated group (N=40) had 2 mg of nicorandil injected into the coronary artery at 2 mm beyond the occlusion with balloon pre-dilation; the sodium nitroprusside-treated group (N=40) underwent the same procedure, but with 200 μg of sodium nitroprusside; the control group (N=40) received PCI and balloon pre-dilation only.

All patients were treated with antiplatelet drugs before primary PCI, including a loading dose of aspirin (300 mg), ticagrelor (180 mg), or clopidogrel (600 mg), as well as atorvastatin (40 mg). Routine coronary angiography and PCI were performed to identify the infarct-related artery (IRA). Initially, the radial artery approach was chosen, and the femoral artery approach was performed only after radial artery puncture failed. Heparin (70 U/kg) was injected through the artery sheath tube before primary PCI.

Patients in the nicorandil-treated group underwent injection of 2 mg nicorandil (Beijing Shihuan Kebao Pharmaceutical Co. Ltd., Beijing, China) into the relevant coronary artery, 2 mm beyond the point of occlusion, with balloon pre-dilation. Patients in the sodium nitroprusside group underwent injection of 200 μg sodium nitroprusside (Huarun Shuanghe Pharmaceutical Co. Ltd., Beijing, China) into the relevant coronary artery, 2 mm beyond the point of occlusion, with balloon pre-dilation. Both drugs were diluted with 0.9% sodium chloride solution to 10 ml; the injection time was 30 seconds. Patients in the control group received an equal volume of 0.9% sodium chloride solution.

If intraoperative blood pressure was less than 90/60 mmHg, or if there was a drop in basal blood pressure of more than 30 mmHg, dopamine was given by intravenous pump. Following

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primary PCI, all patients received treatment with a subcutaneous injection of low molecular weight heparin (LMWH) (4,250 U, 12-hourly) for seven days, and long-term oral aspirin (100 mg, daily), ticagrelor (90 mg, 12-hourly) or clopidogrel (75 mg, daily) for twelve months. Statins were given according to the condition of the patients. Patients with hypertension and diabetes mellitus were treated with routine antihypertensive and hypoglycemic drugs, respectively.

Follow-up measurements of coronary blood flow

The following indices were evaluated by two senior interventional cardiologists, immediately before and after primary PCI: the thrombolysis in myocardial infarction (TIMI) score; the TIMI frame count (TFC); and the TIMI myocardial perfusion grade (TMPG). The TIMI grade was defined as follows: grade 0, no perfusion; grade 1, penetration without perfusion; grade 2, partial perfusion; grade 3, complete perfusion [9].

The TFC was measured as a continuous quantitative objective variable to evaluate an index of coronary flow. The TFC of the left anterior descending (LAD) coronary artery was 1.7-times greater than that of the left circumflex coronary artery (LCCA), and the right coronary artery (RCA) counts. Therefore, the TFC of the longer LAD coronary artery was modified by dividing by 1.7 to obtain the corrected TIMI frame count (cTFC) [9].

The TMPG was defined as follows: grade 0, was defined as no apparent myocardial perfusion in the distribution area of the affected coronary; grade 1, was defined as presence of myocardial a blush with no clearance in the microvasculature; grade 2, was defined as a myocardial perfusion blush that washed out slowly; and grade 3, was defined as a blush that started to clear during washout [10].

Identification of the no-reflow phenomenon (NRP)

The no-reflow phenomenon (NRP) was identified in the cardiac catheterization laboratory during angiography, and was defined as a TIMI flow grade of IRA ≤2, or TIMI flow grade 3, and a TMPG grade ≤2, with the exclusion of mechanical obstruction such as dissection, intimal tear, arterial spasm, and thromboembolism [3].

ECG measurements

A 12-lead ECG was recorded at 90 min following PCI. ST-segment elevation was measured 60 ms after the J point, as the TP segment is the isoelectric interval on the ECG, using the maximum ST-segment elevation. The ST-segment resolution (STR) was defined as: complete STR (CR) ≥70% resolution; partial STR (PR) ≥30% but <70% resolution; or no STR (NR) <30% resolution [11].

Blood chemistry measurements

The level of N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured before, and at one week after, primary PCI. The levels of cTnI and CK-MB were measured before, and every 4 hours following primary PCI, and their peak levels were recorded, with the collection of 2 ml of venous blood during these times. Venous blood samples were placed in a vacuum test tube containing ethylenediaminetetraacetic acid (EDTA) anticoagulant. After mixing the blood sample, hematological analysis was performed using an Alere Triage MeterPro hematology analyzer (Alere, Waltham, MA, USA).

Color Doppler echocardiography

The wall motion score index (WMSI) and left ventricular ejection fraction (LVEF) were calculated by Philips HD15 PureWave (Philips, Amsterdam, Netherlands) color Doppler echocardiography before, and at one week following primary PCI. All patients were required to undergo follow-up measurement of LVEF at one-month following primary PCI.

Main clinical indices and clinical follow-up

Blood pressure and heart rate were measured before and after primary PCI. Intraoperative hypotension was defined as a blood pressure less than 90/60 mmHg or as a drop in basal blood pressure of more than 30 mmHg during the primary PCI procedure. The major adverse cardiovascular events (MACEs) were recorded during hospitalization and three months following primary PCI. The MACEs included life-threatening arrhythmia (ventricular tachycardia and ventricular fibrillation), congestive heart failure, coronary artery revascularization, recurrent MI, and cardiac death [4].

Statistical analysis

Data with a normal distribution were presented as the mean ± standard deviation (SD) and were compared by one-way analysis of variance (ANOVA). Categorical variables were expressed as frequencies and were compared using the Chi-squared test. The Wilcoxon rank-sum test was used for comparison of ranked data. The SPSS 22.0 software package (SPSS, IL, USA) was used for all data analysis. $P<0.05$ was accepted as indicating significance.

Results

Clinical characteristics of the patients

In this study of 120 patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), there were 86 men and

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34 women, with a mean age of 58 years (range, 42–75 years). Three groups were studied, the nicorandil-treated group (N=40), the sodium nitroprusside-treated group (N=40) and the control group (N=40), who received PCI and balloon pre-dilation only.

The differences of the gender, age, body mass index (BMI), previous myocardial infarction (MI), coronary risk factors, blood chemistry, and the Killip class between the three groups were not significant. The differences in the distribution of the infarct-related artery (IRA) and the time from the onset of acute STEMI to primary PCI between the three groups were not significant. The difference between the use of medicines between the three groups was not significant ($P>0.05$) (Table 1).

Procedural characteristics

Before PCI, the differences between the three groups for thrombolysis in myocardial infarction (TIMI) scores, the value of the corrected TIMI frame count (cTFC), and the proportion of TIMI myocardial perfusion grade (TMPG) grade 3 between the three groups were not significant ($P>0.05$). Following PCI, when compared with the control group, the rate of the no-reflow phenomenon (NRP) was significantly lower in the sodium nitroprusside-treated group and the nicorandil-treated group ($P=0.013$). The proportion of cases of TIMI grade 3, TMPG grade 3, and of the complete ST-segment resolution (STR) were greater in the sodium nitroprusside-treated group and nicorandil-treated group compared with those in the control group (all $P<0.05$), while the value of cTFC was significantly lower ($P<0.05$). However, for all the above characteristics there was no significant difference between the sodium nitroprusside-treated group and nicorandil-treated group ($P>0.05$) (Table 2).

Blood chemistry and echocardiography

Before PCI, the levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase-MB (CK-MB), cardiac troponin I (cTnI), wall motion score index (WMSI), and left ventricular ejection fraction (LVEF) showed no significant difference between the three groups ($P>0.05$). Following PCI, the value of NT-proBNP, the peak levels of CK-MB, cTnI and WMSI in the sodium nitroprusside-treated group and the nicorandil-treated group were significantly lower than those in the control group (all $P<0.05$). When compared with the control group, the LVEF at one-week and at one-month following PCI in the sodium nitroprusside-treated group compared with the nicorandil-treated group were significantly increased ($P<0.05$). However, for all the above characteristics there was no significant difference between the sodium nitroprusside-treated group and nicorandil-treated group ($P>0.05$) (Table 3).

Main clinical indices and clinical follow-up

There was no significant difference in the vital cardiovascular measurements (blood pressure and heart rate) between the three groups, before and after primary PCI ($P>0.05$). The rate of intraoperative hypotension in the control group, the sodium nitroprusside-treated group, and the nicorandil-treated group were 12.5% (5/40), 25.0% (10/40) and 5.0% (2/40), respectively, which was a significant difference between the three groups ($P=0.035$). The rate of intraoperative hypotension in the sodium nitroprusside-treated group was significantly greater when compared with the nicorandil-treated group ($P=0.028$). Patients with hypotension were treated with dopamine, but no patient with hypotension required emergency treatment in this study. The incidence of MACEs for patients when in hospital and at three-month follow-up after primary PCI showed no significant difference between the three patient groups ($P>0.05$) (Table 4).

Discussion

Primary percutaneous coronary intervention (PCI) is considered as the most effective treatment for patients with acute ST-segment elevation myocardial infarction (STEMI). The no-reflow phenomenon (NRP) is the inadequate reperfusion of the myocardium in the absence of angiographic evidence of coronary artery obstruction [3]. During the NRP, the ischemic myocardium may be associated with patient symptoms such as chest pain, and electrocardiogram (ECG) changes that include a lack of resolution of ST-segment elevation [5,12]. The mechanism of the NRP may relate to microvascular endothelial damage, microvascular spasm, inflammation, oxidative stress, and thromboembolism, especially microcirculatory obstruction caused by microcirculation structural damage or dysfunction [13,14]. Currently, there are several drugs that have been shown to be effective in the prevention or treatment of reperfusion-related patient outcomes and complications in the NRP, including adenosine, nitroprusside, verapamil, nicorandil, dipyridamole, epinephrine, and cyclosporine [3,15].

Sodium nitroprusside is a direct nitric oxide (NO) donor that has vasodilation, antiplatelet adhesion, and anti-inflammatory effects, and is now a recommended first-line drug for the treatments of the NRP [3,16,17]. The recommended intracoronary dose of sodium nitroprusside is 50–200 μg, with a maximum dose of 1,000 μg [18]. In the previously published study of Hillegass et al., intracoronary administration of sodium nitroprusside (200 μg) rapidly increased the coronary blood flow and significantly reduced the incidence of the NRP [19].

Nicorandil is an ATP-sensitive potassium (KATP) opener that has nitrate-like characteristics and has been recognized as

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Table 1. Clinical characteristics.

	Group A	Group B	Group C	F/χ^2	*P* value
Male (n, %)	26 (65.0)	31 (77.5)	29 (72.5)	1.560	0.459
Age (years)	59±9	60±8	56±7	1.917	0.152
BMI (kg/m^2)	23.1±2.3	22.8±2.1	22.4±2.0	0.933	0.396
Previous MI (n, %)	5 (12.5)	3 (7.5)	5 (12.5)	0.690	0.708
Risk factor (n, %)					
Hypertension	19 (47.5)	24 (60.0)	22 (55.0)	1.276	0.528
Hyperlipoidemia	13 (32.5)	15 (37.5)	16 (40.0)	0.502	0.778
Diabetes mellitus	13 (32.5)	14 (35.0)	17 (42.5)	0.933	0.627
Smoking	14 (35.0)	23 (57.5)	16 (40.0)	4.528	0.104
Blood chemistry					
TC (mg/dl)	183±39	175±36	180±37	0.429	0.652
TG (mg/dl)	73±8	75±9	77±10	1.704	0.186
LDL-C (mg/dl)	118±25	124±25	117±24	1.003	0.370
Blood glucose (mg/dl)	145±8	147±10	143±9	1.650	0.197
HbA1c (%)	6.0±0.5	5.9±0.4	6.0±0.4	0.620	0.540
SCr (mg/dl)	1.11±0.19	1.16±0.21	1.13±0.24	0.612	0.544
Killip class (n, %)				0.117	0.943
I	12 (30.0)	11 (27.5)	13 (32.5)		
II	18 (45.0)	21 (52.5)	18 (45.0)		
III	7 (17.5)	6 (15.0)	7 (17.5)		
IV	3 (7.5)	2 (5.0)	2 (5.0)		
Medicine (n, %)					
Aspirin	40 (100)	40 (100)	40 (100)	–	–
Clopidogrel/ticagrelor	40 (100)	40 (100)	40 (100)	–	–
ACEI/ARB	24 (60.0)	28 (70.0)	29 (72.5)	1.595	0.450
CCB	15 (37.5)	13 (32.5)	17 (42.5)	0.853	0.653
β-blockers	10 (25.0)	15 (37.5)	13 (32.5)	1.463	0.481
Atorvastatin	40 (100)	40 (100)	40 (100)	–	–
Tirofiban	9 (22.5)	6 (15.0)	7 (17.5)	0.779	0.677
Onset-to-balloon time (h)	5.9±1.2	6.3±1.3	5.7±1.1	2.305	0.104
Door-to-balloon time (min)	60±13	63±12	61±13	0.541	0.583
IRA (n, %)				1.937	0.747
RCA	13 (32.5)	16 (40.0)	18 (45.0)		
LAD	19 (47.5)	15 (37.5)	16 (40.0)		
LCX	8 (20.0)	9 (22.5)	6 (15.0)		

n=40 per group. Group A – control group; group B – sodium nitroprusside group; group C – nicorandil group. BMI – body mass index; MI – myocardial infarction; TC – total cholesterol; TG – triglyceride; LDL-C – low-density lipoprotein cholesterol; HbA1c – hemoglobin A1c; SCr – serum creatinine; ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CCB – calcium channel blockers; IRA – infarct-related artery; RCA – right coronary artery; LAD – left anterior descending; LCX – left circumflex.

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Table 2. Procedural characteristics.

	Group A	Group B	Group C	F/χ^2	*P* value
TIMI pre-PCI (n, %)					
0	22 (55.0)	22 (55.0)	19 (47.5)	0.602	0.740
1	11 (27.5)	12 (30.0)	13 (32.5)	0.238	0.888
2	4 (10.0)	4 (10.0)	5 (12.5)	0.173	0.917
3	3 (7.5)	2 (5.0)	3 (7.5)	0.268	0.875
TIMI post-PCI (n, %)					
0	4 (10.0)	0 (0.0)	0 (0.0)	8.276	0.016
1	2 (5.0)	1 (2.5)	1 (2.5)	0.517	0.772
2	6 (15.0)	3 (7.5)	2 (5.0)	2.602	0.272
3	28 (70.0)	36 (90.0)*	37 (92.5)*	9.130	0.010
cTFC pre-PCI	49±12	45±13	44±12	1.810	0.168
cTFC post-PCI	28±6	23±5*	23±5*	13.646	<0.001
TMPG pre-PCI (n, %)					
0	25 (62.5)	23 (57.5)	24 (60.0)	0.208	0.901
1	10 (25.0)	12 (30.0)	11 (27.5)	0.251	0.882
2	3 (7.5)	3 (7.5)	4 (10.0)	0.218	0.897
3	2 (5.0)	2 (5.0)	1 (2.5)	0.417	0.812
TMPG post-PCI (n, %)					
0	7 (17.5)	2 (5.0)	1 (2.5)	6.764	0.034
1	2 (5.0)	1 (2.5)	1 (2.5)	0.517	0.772
2	5 (12.5)	3 (7.5)	2 (5.0)	1.527	0.466
3	26 (65.0)	34 (85.0)*	36 (90.0)*	8.750	0.013
NRP (n, %)	14 (35.0)	6 (15.0)*	4 (10.0)*	8.750	0.013
STR (n, %)					
CR	24 (60.0)	33 (82.5)*	34 (85.0)*	8.276	0.016
PR	9 (22.5	5 (12.5)	5 (12.5)	2.001	0.368
NR	7 (17.5)	2 (5.0)	1 (2.5)	6.764	0.034

n=40 per group. Group A – control group; group B – sodium nitroprusside group; group C – nicorandil group. TIMI – thrombolysis in myocardial infarction; PCI – percutaneous coronary intervention; cTFC – corrected TIMI frame count; TMPG – TIMI myocardial perfusion grade; NRP – no-reflow phenomenon; STR – ST-segment resolution; CR – complete ST-segment resolution; PR – partial ST-segment resolution; NR – no ST-segment resolution. Compared with group A, * $P<0.05$.

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Table 3. Blood chemistry and echocardiography.

	Group A	Group B	Group C	F value	*P* value
NT-proBNP pre-PCI (pg/ml)	1121±244	1087±222	1112±243	0.222	0.801
NT-proBNP 1w post-PCI (pg/ml)	737±133	649±147*	634±146*	6.130	0.003
CK-MB pre-PCI (U/L)	123±37	132±39	117±42	1.349	0.264
CK-MB peak level (U/L)	236±60	201±67*	185±59*	7.223	0.001
cTnI pre-PCI (ng/ml)	2.9±0.8	3.0±1.0	2.7±0.9	0.936	0.395
cTnI peak level (ng/ml)	6.0±1.7	4.8±1.6*	4.7±1.6*	7.256	0.001
WMSI pre-PCI	1.38±0.24	1.40±0.25	1.41±0.26	0.144	0.866
WMSI 1w post-PCI	1.33±0.22	1.22±0.18*	1.24±0.18*	3.571	0.031
LVEF pre-PCI (%)	47±4	48±4	48±5	0.811	0.447
LVEF 1w post-PCI (%)	50±4	52±5*	52±5*	3.569	0.031
LVEF 1m post-PCI (%)	55±4	58±5*	59±5*	5.628	0.005

n=40 per group. Group A – control group; group B – sodium nitroprusside group; group C – nicorandil group. NT-proBNP – N-terminal pro-brain natriuretic peptide; PCI – percutaneous coronary intervention; CK-MB – creatine kinase isoenzyme MB; cTnI – cardiac troponin I; WMSI – wall motion score index; LVEF – left ventricular ejection fraction. Compared with group A, * $P<0.05$.

one of the most important drugs for the treatment of the NRP, with the efficacy of nicorandil in the setting of myocardial reperfusion injury having been previously reported [15]. Chen et al. analyzed intracoronary administration of nicorandil (2 mg) and showed that it could effectively treat the NRP [4]. In a previously published study by Kostic et al., intracoronary administration of nicorandil in patients with STEMI undergoing primary PCI significantly improved microvascular function by reducing the microvascular resistance index and increasing coronary flow reserve [20].

In the present study, when compared with the control grop, the incidence of the NRP and the value of the corrected thrombolysis in myocardial infarction (TIMI) frame count (cTFC) were significantly lower in the sodium nitroprusside-treated group compared with the nicorandil-treated group (P=0.013), while the proportion of TIMI grade 3 and TIMI myocardial perfusion grade (TMPG) grade 3 were significantly greater (P=0.010 and 0.013, respectively). There were no significant difference between the sodium nitroprusside-treated group and the nicorandil-treated group.

The TIMI flow grade reflects epicardial blood perfusion, and the TMPG reflects myocardial perfusion [4]. Therefore, the findings of the present study suggest that prophylactic intracoronary administration of nicorandil can effectively reduce the incidence rate of the NRP and that nicorandil has effects that are equal to those of sodium nitroprusside. This finding may be explained by the fact that nicorandil can open the KATP channel, inhibit sarcolemmal calcium release, decrease the intracellular concentration of calcium, dilate the coronary arteries, reduce microvascular resistance, and improve myocardial microcirculation [4,20,21]. Also, nicorandil can activate guanylate cyclase in vascular smooth muscle cells, increase the concentration of cyclic guanosine monophosphate (cGMP) in the cell through its metabolite NO, relax the coronary arteries, and increase the blood flow in the coronary arteries [22]. During PCI, the effects of the balloon passing the intracoronary lesion, with balloon dilation, stent implantation and atherosclerotic plaque rupture, vasoconstrictive and vasoactive substances are released into the blood, resulting in distal coronary microvascular spasm, microcirculation obstruction, and an increased incidence of the NRP. Due to balloon dilation, blood flows through the previously occluded coronary artery, and drugs may more rapidly reach the coronary microvasculature and to achieve therapeutic blood concentrations. Currently, the intracoronary administration of nicorandil following balloon dilation and before the occurrence of the NRP could dilate coronary microvasculature and increase blood flow more quickly to prevent the microvascular spasm caused by stent implantation and reduce the incidence of the NRP caused by microcirculatory disturbance.

The NRP is a marker of myocardial injury, ischemia, and infarction, as well as a predictor of ventricular remodeling and cardiac insufficiency. In the previously published study by Durante et al., patients with the NRP had a lower LVEF following PCI, while the incidence of MACEs was high [23]. In the present study, compared with the control group, the value of N-terminal pro-brain natriuretic peptide (NT-proBNP), creatine kinase-MB

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Table 4. Main clinical index and follow-up.

	Group A	Group B	Group C	F/χ^2	*P* value
HR pre-PCI (bpm)	73±7	72±7	75±8	1.957	0.146
HR post-PCI (bpm)	67±7	64±6	65±7	1.334	0.267
BP pre-PCI (mmHg)					
SBP	109±11	107±12	108±11	0.558	0.574
DBP	68±7	66±7	67±7	0.549	0.579
MAP	81±8	80±8	80±8	0.517	0.598
BP post-PCI (mmHg)					
SBP	120±10	119±11	123±12	1.521	0.223
DBP	74±7	72±8	75±7	2.024	0.137
MAP	89±8	87±8	91±8	1.997	0.140
Intraoperative hypotension (n, %)	5 (12.5)	10 (25.0)	2 (5.0)*	6.716	0.035
MACEs in hospital (n, %)					
Total	5 (12.5)	3 (7.5)	0 (0.0)	5.089	0.079
Congestive heart failure	2 (5.0)	2 (5.0)	0 (0.0)	2.069	0.355
Malignant arrhythmia (VT, VF)	3 (7.5)	1 (2.5)	0 (0.0)	3.621	0.164
Reccurent MI	0 (0.0)	0 (0.0)	0 (0.0)	–	–
TVR	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Death	0 (0.0)	0 (0.0)	0 (0.0)	–	–
MACEs three-month (n, %)					
Total	7 (17.5)	5 (12.5)	1 (2.5)	4.831	0.089
Congestive heart failure	2 (5.0)	1 (2.5)	1 (2.5)	0.517	0.772
Malignant arrhythmia (VT, VF)	2 (5.0)	1 (2.5)	0 (0.0)	2.051	0.359
Reccurent MI	1 (2.5)	0 (0.0)	0 (0.0)	2.017	0.365
TVR	2 (5.0)	2 (5.0)	0 (0.0)	2.069	0.355
Death	0 (0.0)	1 (2.5)	0 (0.0)	2.017	0.365

n=40 per group. Group A – control group; group B – sodium nitroprusside group; group C – nicorandil group. HR – heart rate; PCI – percutaneous coronary intervention; BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; MAP – mean arterial pressure; MACEs – major adverse cardiovascular events; VT – ventricular tachycardia; VF – ventricular fibrillation; MI – myocardial infarction; TVR – target vessel revascularization. Compared with group B, * $P<0.05$.

(CK-MB), cardiac troponin I (cTnI), and wall motion score index (WMSI) in the nicorandil-treated group were significantly lower, while the cases of complete ST-segment resolution (STR) and LVEF were significantly greater. These findings suggested that nicorandil could promote the recovery of the myocardium. This conclusion is supported by the findings of the recently published study by Pang et al., who showed that nicorandil exerted its cardioprotective effects by decreasing PCI-related myocardial injury, reducing the rate of the NRP and improving LVEF [7]. Izumiya et al. showed that nicorandil could improve endothelial function and cardiac sympathetic nerve activity, prevent inflammation and oxidative stress, improve fibrinolytic ability, and stabilize arterial atheromatous plaques [24]. Kostic and Li have suggested that nicorandil might activate the NO-protein kinase G (PKG) pathway, open the mitochondrial KATP channel, inhibit the opening of the mitochondrial

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permeability transition pore (mPTP), simulate myocardial ischemic preconditioning, and improve myocardial cell metabolism [20,22]. Recently published studies by Campo et al. and Bonora et al. found that the Fo ATP synthase C subunit serum levels and F1FO-ATP synthase dimers were significantly related to myocardial reperfusion [25,26]. A recent meta-analysis by Campo et al. has shown that drugs that target mitochondrial function, when used as an adjunct to reperfusion in STEMI patients undergoing primary PCI, reduced hospital readmission for heart failure [27]. Therefore, the application of nicorandil before the occurrence of the NRP has the potential to improve cardiac function and prognosis following primary PCI for acute STEMI.

One of the findings from this study in 120 patients at a single center was that the incidence of episodes of intraoperative hypotension in the sodium nitroprusside-treated group was greater when compared with the nicorandil-treated group. This finding may be explained by the fact that intracoronary administration of nicorandil leads to the release of a small dose of the drug into the systemic circulation, but that the vasodilatory effect of sodium nitroprusside is greater than that of nicorandil [28]. Because hypotension usually occurs after acute STEMI, sodium nitroprusside, which is more likely to reduce blood pressure, is of limited value in treating patients with hypotension. Therefore, nicorandil is more suitable than sodium nitroprusside for the treatment of patients with acute STEMI.

Intracoronary drug administration is considered to be a better method than intravenous administration for the prevention and treatment of the NRP due to the higher drug concentration in the affected coronary artery [3]. However, the traditional method of injecting the drug through the guide catheter into the coronary artery orifice has several disadvantages, including overflow to the aortic root and drug administration to non-affected coronary vessels [29]. The present study used a method that included a pre-dilation balloon to inject the drugs beyond the point of occlusion, which was shown to avoid the disadvantages of intracoronary drug administration, ensure high drug concentration in affected areas of myocardial ischemia and infarction, and reduce the systemic effects of the drugs. The findings of this study have shown that intracoronary nicorandil treatment on the NRP during primary PCI in patients with acute STEMI enabled the affected coronary artery to undergo rapid recovery of blood flow with almost no influence on blood pressure, indicating that this is a safe and effective method of drug administration.

Conclusions

The findings of this study showed that patients with sustained acute ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), treated with intracoronary nicorandil, had a reduced incidence of the no-reflow phenomenon (NRP), improved myocardial perfusion and cardiac function, and that intracoronary nicorandil was not associated with a significant lowering of blood pressure.

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