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Effects of nicorandil on systemic inflammation and oxidative stress induced by percutaneous coronary intervention in patients with coronary heart disease

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Abstract

Objective: The present study investigated the effects of a bolus intracoronary injection of nicorandil on systemic inflammation and oxidative stress induced by percutaneous coronary intervention (PCI) in patients with coronary heart disease (CHD).

Methods: Patients undergoing coronary angiography (CAG) were enrolled into the CAG group (n = 30). Patients undergoing PCI were randomly divided into the PCI (n = 30) and PCI + nicorandil groups (n = 30).

Results: Blood taken from patients in the placebo group 24 hours after PCI exhibited significant increases in the expression of inflammatory indicators and mild increases in the expression of anti-inflammatory indicators. The intracoronary injection of nicorandil reversed the elevation of

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inflammatory indicators and significantly increased the levels of anti-inflammatory indicators in the blood of patients with PCI. Blood taken from patients in the placebo group 24 hours after PCI also displayed significant decreased superoxide dismutase levels and increased malondialdehyde levels. Nicorandil treatment reversed these changes of oxidative stress marker levels.
Conclusions: These results indicated the possible medical application of intracoronary injections of nicorandil for reducing systemic inflammation and oxidative stress in the peripheral blood of patients undergoing PCI.

Keywords
Nicorandil, percutaneous coronary intervention, inflammation, oxidative stress, coronary heart disease, coronary angiography

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Introduction

Coronary heart disease (CHD) has become a major cause of death and disability globally. Percutaneous coronary intervention (PCI) is recognized as one of the most effective and essential methods for patients with acute myocardial infarction (AMI) or unstable angina (UA). Compared with the effects of traditional drug therapy, PCI can more effectively improve coronary blood flow, restore myocardial perfusion, reduce myocardial ischemia or the infarction area, and improve clinical prognoses.[1,2] However, some patients with AMI or UA do not benefit from PCI because of myocardial no-reflow (MNR).[3]

The absence of MNR, which is also called coronary stent reflux, is considered a manifestation of coronary function disorders during the reperfusion of acute myocardial ischemia. Mechanical injury induced by PCI might increase inflammation and oxidative stress, which may participate in MNR.[3] It has been revealed that inflammation and reactive oxygen species (ROS) can cause the constriction of capillaries under ischemic conditions and participate in the phenomenon of MNR.[4,5] Previous research demonstrated that MNR is related to the poor prognosis in patients with AMI after PCI, as typified by cardiac dysfunction, arrhythmia, and myocardial injury.[6] Thus, it is urgent to identify an effective and feasible therapeutic method for preventing MNR in patients with CHD undergoing PCI. Multiple interventions have been clinically used to rescue MNR, including mechanical methods such as intra-aortic balloon pumping or post-conditioning, and pharmacological agents including adenosine, nitroprusside, verapamil, nicorandil, dipyridamole, epinephrine, and cyclosporine.[7–9]

Nicorandil is an ATP-sensitive potassium channel (K_{ATP}) opener than can improve the dilation of macro- and microvessels to protect the myocardium in patients with acute coronary syndrome (ACS).[10] Recently, several studies described the safety of the intravenous or intracoronary injection of nicorandil and its efficacy in improving myocardial perfusion during PCI.[10–13] Nicorandil also reduces the incidence of MNR, thereby reversing the possible poor prognosis of patients undergoing PCI.[10,13] Furthermore, nicorandil administration at the time of primary PCI was

associated with reduced rates of major adverse cardiovascular events (MACE) both in the hospital and after discharge.[14] Previous studies demonstrated that nicorandil plays a protective role in ischemia–reperfusion myocardial injury as a K_{ATP} opener. Nicorandil expanded coronary microcirculation through inducing the opening of K_{ATP} channels, which are abundantly expressed in arterial smooth muscle cell membranes with a diameter of approximately 100 μm.[12] Meanwhile, nicorandil reduced endothelial function damage caused by the coronary stent-coating drugs paclitaxel and sirolimus by inducing the opening of mitoK_{ATP} channels, which may exert a protective effect through inhibiting oxidative stress.[15] However, the potential mechanism by which nicorandil reduces MNR during PCI, in addition to dilating coronary arteries, remains unclear. In this study, we investigated the association of a bolus intracoronary injection of nicorandil during PCI with the serum levels of inflammatory and oxidative stress indicators in patients to verify the underlying mechanism by which nicorandil reduces the incidence of MNR.

Materials and methods

Study population

Patients who were hospitalized in the Department of Cardiology of our hospital because of chest pain and who underwent coronary angiography (CAG) were eligible for study. Patients with ACS included those with acute ST segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and UA. The exclusion criteria were as follows: older than 90 years or younger than 30 years, history of PCI or coronary artery bypass graft, systolic blood pressure <88 mmHg, allergy to nicorandil or clopidogrel/ticagrelor, bleeding history in the prior 3 months, malignant tumors, hepatic impairment, renal insufficiency, primary or secondary thrombocytopenia or platelet dysfunction, moderate-to-severe anemia, and acute heart failure. Patients with NSTEMI are not eligible for stent implantation; thus, they were also excluded.

This study protocol was approved by our Hospital Ethics Committee (approval number: KYLL–2015266; Approval date: February 25, 2015) and registered with Current Controlled Trials (registration number: ChiCTR1800019349, registration date: November 7, 2018). All enrolled patients provided written informed consent to participate in this trial. Patients who underwent PCI were randomly assigned to the PCI or PCI + nicorandil group on a 1:1 basis. All procedures were performed as standard interventional techniques following current guidelines at the time of intervention.

Outline of the study procedures

CAG was performed in patients to visualize the severity of stenosis in coronary arteries. PCI was then performed if the residual diameter of stenosis was equal to or greater than 75% of the coronary artery diameter. Patients received an intracoronary bolus injection of 2 mg of nicorandil (1 mg/mL) or an equal volume of placebo (2 mL of 0.9% saline) into the coronary ostia 2 mm beyond the occlusion prior to PCI. Peripheral blood samples were collected before CAG and 24 hours after CAG (Figure 1 and Supplementary Figure 1).

Blood sample collection

Approximately 10 mL of peripheral venous blood samples were collected from all participants before and 24 hours after CAG. All samples were collected in Vacutainer anticoagulant tubes (BD, Franklin Lakes, NJ, USA). Blood samples placed in separate centrifuge tubes were then centrifuged at $3000 \times g$ for 10 minutes to obtain both

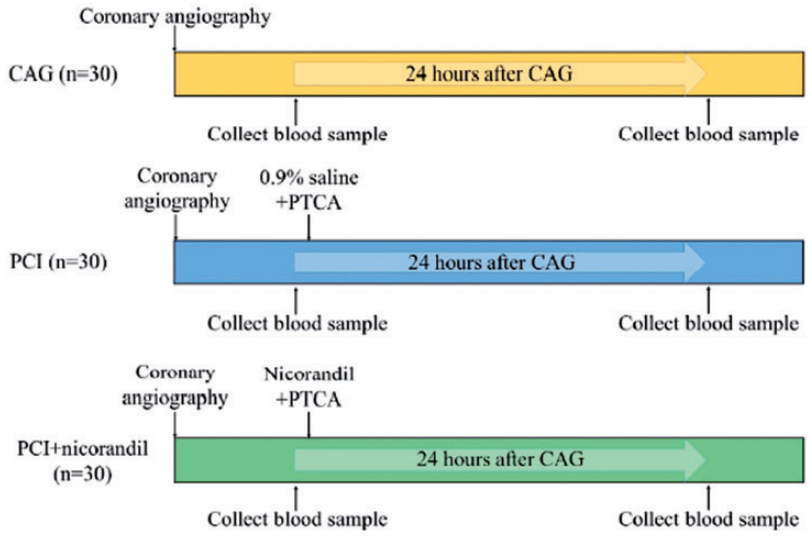

Figure 1. Protocol of the study. Patients with chest pain who underwent CAG were included in this trial. Patients were randomly assigned to receive an intracoronary injection of nicorandil or the same volume of 0.9% saline.
CAG, coronary angiography; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

serum and plasma, which were immediately aliquoted and frozen at −80°C for further analysis. Serum was used to test the expression of C-reactive protein (CRP), tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-1β, IL-1 receptor A (IL-1RA), IL-6, IL-10, IL-13, and superoxide dismutase (SOD). Plasma was used to examine the levels of malondialdehyde (MDA).

Cytokine detection

Enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MA, USA) were used to detect the expression of cytokines, including CRP, TNF-α, MCP-1, IL-1β, IL-1RA, IL-6, IL-10, and IL-13, in serum or plasma according to the manufacturer's instructions. The levels of all cytokines were calculated using the ELISA standard curve, which was produced via serial dilution with the standards. The absorbance of the samples was determined at 450 on a SpectraMax Plus 384 Microplate Reader (Molecular Devices, San Jose, CA, USA).

Measurement of SOD

The expression of SOD was examined using an SOD determination kit (Sigma-Aldrich, St. Louis, MO). All procedures were performed according to the manufacturer's instructions. The absorbance was read at 450 nm using a microplate reader. Three replicates were conducted for each sample.

Measurement of MDA

MDA levels were examined using a Lipid Peroxidation Assay Kit (Sigma-Aldrich) according to the manufacturer's instructions. The MDA standard solution was used to create a standard curve. The absorbance was measured at 532 nm using a microplate reader. Each sample performed three replicates.

Statistical analysis

All experiments were repeated three times, and the values were averaged. Data were presented as the mean ± standard error of the mean. SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Comparisons between two groups were assessed using a two-sided unpaired Student *t*-test for normally distributed variables. Comparison of ≥3 groups were performed via one-way analysis followed by post hoc analysis with Dunnett's multiple comparison test as appropriate. All data in this study were identified to follow a normal Gaussian distribution after a normality test. $P < 0.05$ indicated statistical significance.

Results

Patient baseline characteristics

Ninety patients were enrolled, 30 of whom underwent CAG without PCI. The other 60 patients were randomly divided into the PCI and PCI + nicorandil groups on a 1:1 basis. The baseline characteristics of patients in the three groups are presented in Table 1. There were no differences in age, sex, body mass index, systolic blood pressure, diastolic blood pressure, heart rate, and cardiovascular risk factors, including the percentage of smokers and histories of diabetes, hypertension, and hyperlipidemia, among the groups. In addition, white blood cells and platelet counts and hemoglobin, alanine transaminase, aspartate aminotransferase, creatinine, blood urea nitrogen, fasting blood glucose, and lipid levels were similar among the groups (Table 2).

Effect of nicorandil on pro-inflammatory cytokine levels after PCI

We tested the expression of pro-inflammatory cytokines, including CRP, TNF-α, MCP-1, IL-1β, and IL-6, in the venous blood of patients before and 24 hours after CAG. We found no significant differences in the expression of all pro-inflammatory cytokines among the three groups before CAG. In the PCI group, the expression of pro-inflammatory cytokines, including CRP, TNF-α, IL-1β, and IL-6, was markedly elevated 24 hours after PCI compared with that after CAG (all $P < 0.05$, Figure 2a–2d). Furthermore, patients in the PCI + nicorandil group displayed significant reductions in the expression of these inflammatory factors

Table 1. Clinical characteristics of the study population.

Characteristics	CAG group (n = 30)	PCI group (n = 30)	PCI + nicorandil group (n = 30)	*P*
Male, n	21	22	22	>0.05
Age (years)	59.33 ± 16.46	57.93 ± 18.03	55.90 ± 17.05	>0.05
BMI (kg/m^2)	25.7 ± 4.49	24.80 ± 4.91	24.28 ± 4.01	>0.05
Cardiovascular risk factors				
Hypertension, n	18	19	18	>0.05
Diabetes, n	15	16	17	>0.05
Smoking, n	10	9	11	>0.05
Systolic BP (mmHg)	139.5 ± 12.1	140.5 ± 13.5	142.7 ± 11.2	>0.05
Diastolic BP (mmHg)	82.8 ± 12.1	79. 9 ± 10.5	81.7 ± 13.5	>0.05
Heart rate (bpm)	77.2 ± 12.2	76.2 ± 12.6	74.1 ± 15.0	>0.05

BMI, body mass index; BP, blood pressure; CAG, coronary angiography; PCI, percutaneous intervention.

Table 2. Hematological indicators of participants in the three groups.

Parameters	CAG group (n = 30)	PCI group (n = 30)	PCI + nicorandil group (n = 30)	*P*
WBC (10^9/L)	6.00 ± 1.86	6.64 ± 1.87	6.25 ± 1.76	>0.05
Hemoglobin (g/L)	151.20 ± 13.86	150.93 ± 11.74	155.30 ± 11.23	>0.05
Platelet (10^9/L)	194.43 ± 64.09	196.17 ± 61.92	203.9 ± 65.18	>0.05
ALT (U/L)	29.13 ± 13.08	28.6 ± 13.79	28.63 ± 11.79	>0.05
AST (U/L)	26.83 ± 7.19	27.53 ± 8.08	27.73 ± 8.36	>0.05
Creatinine (μmol/L)	84.28 ± 11.94	80.78 ± 14.89	87.16 ± 12.97	>0.05
BUN (mmol/L)	5.61 ± 1.49	5.33 ± 1.59	5.64 ± 1.43	>0.05
FBG (mmol/L)	6.10 ± 2.29	6.08 ± 2.32	6.78 ± 3.33	>0.05
TC (mmol/L)	3.92 ± 0.96	4.20 ± 0.94	3.75 ± 0.10	>0.05
TG (mmol/L)	1.35 ± 0.66	1.48 ± 0.63	1.40 ± 0.62	>0.05
LDL-C (mmol/L)	2.46 ± 0.80	2.69 ± 0.78	2.35 ± 0.84	>0.05
HDL-C (mmol/L)	1.18 ± 0.21	1.21 ± 0.27	1.16 ± 0.25	>0.05

WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CAG, coronary angiography; PCI, percutaneous coronary intervention.

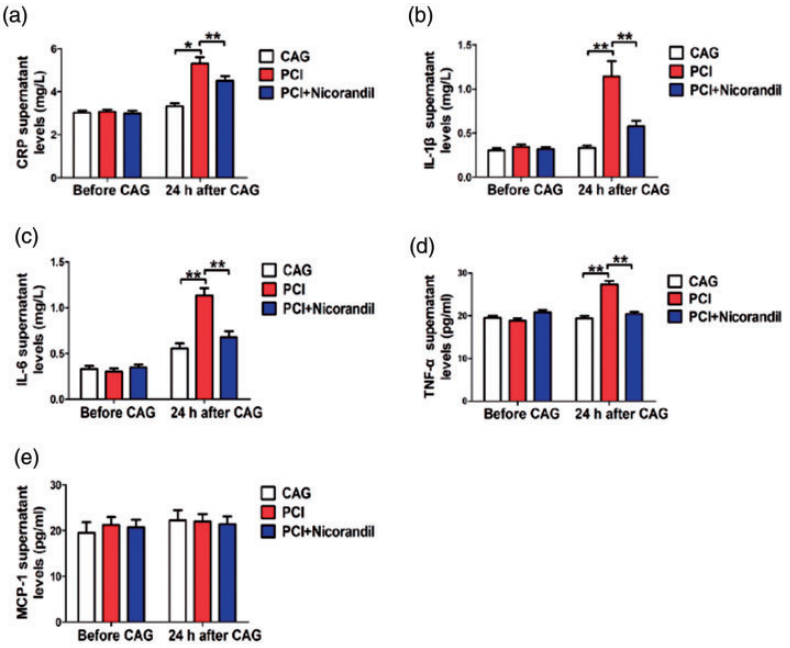

Figure 2. Effect of nicorandil on pro-inflammatory cytokine levels. (a) CRP levels in the three groups before and 24 hours after CAG. (b) IL-1β levels in the three groups before and 24 hours after CAG. (c) IL-6 levels in the three groups before and 24 hours after CAG. (d) TNF-α levels in the three groups before and 24 hours after CAG. (e) MCP-1 levels in the three groups before and 24 hours after CAG. Values are expressed as the mean ± standard error of the mean. *$P < 0.05$, **$P < 0.01$.
PCI, percutaneous coronary intervention; CAG, coronary angiography; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; MCP-1, monocyte chemotactic protein 1.

24 hours after PCI compared with the findings in the PCI group (all $P < 0.05$, Figure 2a–2d). However, MCP-1 expression did not differ among the groups either before or after CAG (Figure 2e). Nicorandil may alleviate inflammation by reducing the upregulation pro-inflammatory indicators induced by PCI.

Effect of nicorandil on anti-inflammatory cytokine levels after PCI

We also tested the expression of anti-inflammatory cytokines, including IL-1RA, IL-10, and IL-13, in the venous blood of patients before and 24 hours after CAG. We found no significant difference in the expression of all anti-inflammatory cytokines among the three groups of patients before CAG. In the PCI group, the expression of anti-inflammatory cytokines, including IL-1RA, IL-10, and IL-33, was mildly increased 24 hours after PCI versus that after CAG (all $P < 0.05$, Figure 3a–3c). Patients in the PCI + nicorandil group displayed significantly elevated expression of anti-inflammatory factors 24 hours after PCI compared with the findings in the PCI group (all $P < 0.01$, Figure 3a–3c). Nicorandil may alleviate inflammation by upregulating anti-inflammatory indicators in patients who underwent PCI.

Effect of nicorandil on oxidative stress after PCI

We further tested the levels of oxidative stress indicators, including SOD and MDA, in the venous blood of patients

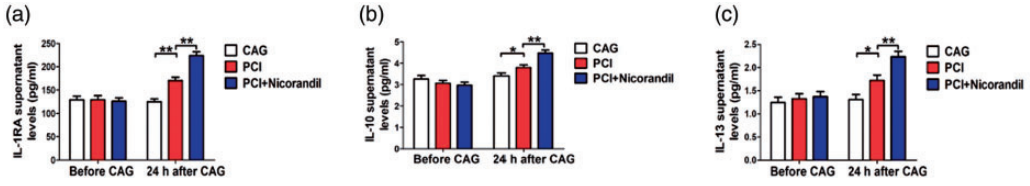

Figure 3. Effect of nicorandil on anti-inflammatory cytokine levels. (a) IL-1RA levels in the three groups before and 24 hours after CAG. (b) IL-10 levels in the three groups before and 24 hours after CAG. (c) IL-13 levels in the three groups in three groups before and 24 hours after CAG. Values are expressed as the mean ± standard error of the mean. *$P < 0.05$, **<0.01.
PCI, percutaneous coronary intervention; CAG, coronary angiography; IL, interleukin; IL-1RA, interleukin-1 receptor A.

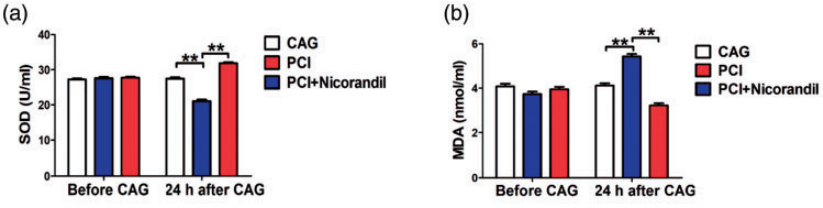

Figure 4. Effect of nicorandil on the levels of oxidative stress indicators. (a) Levels of SOD in the three groups before and 24 hours after CAG. (b) Levels of MDA in the three groups before and 24 hours after CAG. Values are expressed as the mean ± standard error of the mean. **$P < 0.01$.
PCI, percutaneous coronary intervention; CAG, coronary angiography; SOD, superoxide dismutase; MDA, malondialdehyde.

before and 24 hours after CAG. We identified no differences in the levels of SOD and MDA among the three groups before CAG. The expression of SOD was reduced in patients 24 hours after PCI versus that after CAG ($P < 0.01$, Figure 4a), and nicorandil treatment significantly increased the expression of SOD 24 hours after PCI ($P < 0.01$, Figure 4a). Conversely, MDA levels were increased in patients 24 hours after PCI ($P < 0.01$ vs. 24 hours after CAG, Figure 4b), and this change was significantly reversed by nicorandil treatment ($P < 0.01$ vs. 24 hours after PCI, Figure 4b). These results indicated that nicorandil treatment reduces ROS levels, thereby improving oxidative stress in patients who underwent PCI.

Discussion

The present investigation found that an intracoronary injection of nicorandil alleviated the inflammatory reaction and oxidative stress in the peripheral blood in patients 24 hours after PCI. We found that an intracoronary bolus injection of nicorandil could significantly decrease the expression of pro-inflammatory cytokines and elevate that of anti-inflammatory indicators in patients 24 hours after PCI compared with the findings in patients who underwent PCI alone. Meanwhile, oxidative stress, which was enhanced following PCI, was alleviated in patients who received nicorandil. These results indicated that nicorandil might prevent MNR by regulating inflammatory responses and oxidative stress induced by PCI.

Recent studies revealed that inflammation and oxidative stress may be essential for the mechanism of MNR in patients with ACS after PCI.[16] After the reperfusion of myocardial ischemia, myocardial inflammatory factors and ROS, both of which caused myocardial injury and cardiac dysfunction,[17] were detected. On the one hand, PCI induced the shedding of atherosclerotic plaques, thereby potentially inducing myocardial inflammation,[18] which has been considered an important cause of significant ventricular dysfunction.[3,19] The release of massive amounts of inflammatory mediators, such as TNF-α and IL-1β, plays an important role in the development and progression of MNR.[20] On the other hand, ROS were generated and released after reperfusion because of damage of the mitochondrial respiratory chain.[21] The accumulation of ROS in the body caused oxidative damage, which may further aggravate MNR.[22]

In this study, we investigated a cohort of patients undergoing either CAG or PCI with or without an intracoronary injection of nicorandil and examined the changes of serum pro-inflammatory and anti-inflammatory cytokines between before and 24 hours after intervention. The results indicated that the serum levels of pro-inflammation cytokines, excluding MCP-1, rose sharply 24 hours after PCI. These results indicated the presence of systemic inflammation in patients who underwent PCI, reflecting a short inflammatory response of the body to invasive procedures.[23] Surprisingly, we also found mild increases in the serum levels of the anti-inflammatory indicators IL-1RA, IL-10, and IL-13. This suggests the presence of an underlying feedback mechanism of the body to counteract pro-inflammatory stimulation.[24,25] Previous research found that an intracoronary bolus of nicorandil could improve the instantaneous increases of inflammation and oxidative stress in the coronary blood of patients with ACS during PCI.[21] This investigation demonstrated that an intracoronary injection of nicorandil could further ameliorate the inflammatory and oxidative reactions in peripheral blood, which supported the need for a longer treatment period for nicorandil.

Nicorandil is a nitrate-like and ATP-sensitive potassium channel opener that can dilate coronary arteries and participate in ischemic pre-conditioning for cardioprotection.[26] Studies demonstrated the anti-inflammatory properties of nicorandil.[21,27] Intracoronary nicorandil has proven safe clinically.[10–13] This trial found that nicorandil significantly reduced the levels of pro-inflammatory indicators, including CRP, IL-1β, IL-6, and TNF-α, 24 hours after PCI. Furthermore, the drug also elevated the levels of anti-inflammatory cytokines, including IL-1RA, IL-10, and IL-13, 24 hours after PCI. Thus, the use of nicorandil during PCI may be effective for reducing the inflammatory reaction, thereby protecting against MNR.

K_{ATP} regulates the production of ROS, and nicorandil can reduce oxidative stress by preventing endothelial function damage caused by the coronary stent-coating drugs sirolimus and paclitaxel *in vivo*.[21,28] SOD and MDA levels directly reflect the levels of ROS. Our results revealed that blood taken from patients 24 hours after PCI displayed significantly increased SOD levels and decreased MDA levels. Nicorandil treatment reversed the induction of oxidative stress in the blood of patients with PCI. Thus, the use of nicorandil during PCI may be effective for reducing the oxidative stress and preventing MNR.

Previous studies reported that the phenomenon of MNR was believed to be associated with impaired cardiac microvascular function including microcirculatory barrier function, endothelial damage, inflammation, and increased oxidative stress.[29] The release of both pro-inflammatory mediators, such as TNF-α and IL-1β, and ROS plays an important role in the development and progression of MNR.[30] We found that nicorandil could improve inflammation and oxidative stress, which may participate in MNR, in addition to its effect on vasodilation in this trail. Thus, the suppression of MNR by nicorandil might occur through the inflammatory pathway. Necessary animal and cell experiments should be performed to further confirm the relationship of the inflammatory pathway induced by nicorandil and the reduction of MNR.

This study had several limitations, including the small sample sizes of the three groups. We initially assessed and assured the normality of the data distribution and then performed power analysis through PASS based on the levels of CRP, IL-1β, IL-6, TNF-α, IL-1RA, IL–33, SOD, and MDA. The value of $1 - \beta$ exceeded 0.8 among the three groups of patients based on the aforementioned data. Second, we reviewed the MACE of the enrolled patients during hospitalization. No patients experienced in-hospital MACE, including cardiac death, non-fatal myocardial infarction, and repeat revascularization. However, we lack the follow-up data and records of adverse reactions of patients enrolled in this investigation. Further investigations are indeed necessary and urgent to obtain more detailed in-hospital and follow-up data and records of adverse reactions based on the use of nicorandil in patients during PCI.

In conclusion, our investigation revealed that an intracoronary injection of nicorandil alleviates inflammation and oxidative stress in patients with CHD after PCI. Thus, nicorandil might regulate inflammatory responses and oxidative stress to improve coronary microcirculation in addition to its dilatory effects on coronary arteries to prevent coronary no-reflow.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

YZ, JL, and LL conceived, designed, and performed the experiments. LK, LC, XX, and LL collected and analyzed the data. All authors contributed to the interpretation of data and drafting or revision of the paper. All authors read and approved the manuscript and agreed to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work is appropriately investigated and resolved.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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