

Myocardial protective effect of intracoronary administration of nicorandil and alprostadil via targeted perfusion microcatheter in patients undergoing elective percutaneous coronary intervention

A randomized controlled trial

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Abstract

Background: The aim of the study was to evaluate the efficacy of nicorandil and alprostadil on myocardial protection in patients undergoing elective percutaneous coronary intervention (PCI).

Methods: In this prospective, single-blinded, randomized controlled study, 90 consecutive patients scheduled for elective PCI for *de novo* coronary lesions were assigned to the nicorandil, alprostadil, and nitroglycerin groups in a 1:1:1 ratio. Drugs were administered intracoronary via a targeted perfusion microcatheter. The primary endpoint was the thrombolysis in myocardial infarction (TIMI) myocardial perfusion frame count (TMPFC). Additionally, the corrected TIMI frame count (cTFC), TIMI myocardial perfusion grade (TMPG), and incidence of periprocedural myocardial injury (PMI) were assessed.

Results: Both nicorandil and alprostadil were significantly effective in reducing TMPFC (114.6 ± 33.7 vs 93.4 ± 30.9 , $P = .016$; 114.3 ± 34.3 vs 94.7 ± 33.3 , $P = .029$, respectively). Similar findings were observed in the improvement of cTFC (20.3 ± 10.5 vs 13.5 ± 5.0 , $P = .003$; 20.2 ± 7.4 vs 15.2 ± 5.2 , $P = .003$, respectively) and percentage of TMPG 3 (100% vs 82.8%, $P = .052$; 83.3% vs 96.7%, $P = .196$, respectively); whereas, nitroglycerin produced a limited effect on TMPFC (114.4 ± 30.9 vs 112.1 ± 31.9 , $P = .739$), cTFC (19.4 ± 7.2 vs 19.3 ± 7.2 , $P = .936$), and percentage of TMPG 3 (86.7% vs 86.7%, $P = 1.000$). No significant difference was found in the incidence of PMI (16.7% vs 16.0% vs 27.6%, $P = .537$), though it was comparatively lower in the nicorandil and alprostadil groups. Furthermore, the intracoronary administration of nicorandil and alprostadil had a mild effect on blood pressure and heart rate.

Conclusions: The intracoronary administration of nicorandil and alprostadil via a targeted perfusion microcatheter was more effective in improving myocardial perfusion in patients undergoing elective PCI than nitroglycerin.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor, ACS = acute coronary syndrome, ARB = angiotensin receptor blocker, ATP = adenosine triphosphate, cTFC = corrected TIMI frame count, cTnI = cardiac troponin I, LAD = left anterior

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

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descending artery, LCX = left circumflex artery, PCI = percutaneous coronary intervention, PGE1 = prostaglandin E1, PMI = periprocedural myocardial injury, RCA = right coronary artery, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction, TMPFC = TIMI myocardial perfusion frame count, TMPG = TIMI myocardial perfusion grade, URL = upper reference limit.

Keywords: alprostadil, elective percutaneous coronary intervention, myocardial perfusion, nicorandil, periprocedural myocardial injury, targeted perfusion microcatheter

1. Introduction

Percutaneous coronary intervention (PCI) has become the predominant treatment for coronary revascularization within the past few decades. Innovations in the techniques make it a safer and more successful procedure, especially in elective settings.^[1,2] Nevertheless, approximately 7%–40% of patients undergoing elective PCI suffer periprocedural myocardial injury (PMI), which is associated with an increased risk of adverse outcomes.^[3,4]

In addition to procedure-related complications including side-branch occlusion or dissection, PMI is mostly thought to be caused by microvascular obstruction.^[5] To address this issue, different strategies have been proposed to increase cardiac tolerance to ischemic injury. Nicorandil, a potent coronary vasodilator with both nitrate-like and ATP-sensitive potassium channels (K^+ ATP), alleviates coronary no-reflow or slow-flow phenomenon in patients with acute ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.^[6–9] Consequently, alprostadil, a liposomal drug, is also reported to be effective in myocardial protection in the same case.^[10] However, the efficacy of nicorandil and alprostadil on myocardial perfusion remains unknown in patients undergoing elective PCI.

In this study, we evaluated whether the intracoronary administration of nicorandil, alprostadil, and nitroglycerin via a targeted perfusion microcatheter was beneficial in ameliorating myocardial perfusion in patients with non-acute coronary syndrome (ACS) undergoing elective PCI. The incidence of PMI was also assessed to determine the effects of these drugs on myocardial protection.

2. Methods

2.1. Study population

Patients with non-ACS, who planned to undergo elective PCI for *de novo* coronary lesions, were admitted to the Cardiac Center of Shanghai Chest Hospital affiliated to Shanghai Jiao Tong University from May 2019 to May 2020. Among them, those with single-vessel disease and thrombolysis in myocardial infarction (TIMI) grade 3 following PCI were included in this study. Exclusion criteria were as follows: i) contraindication of intracoronary nicorandil or alprostadil administration; ii) elevated cardiac troponin I (cTnI) at baseline; iii) left main disease or bifurcation lesion requiring side-branch intervention or chronic total occlusion; iv) history of myocardial infarction or coronary artery bypass grafting; v) pregnancy; and vi) other complications, including cardiac shock, severe arrhythmia, end-stage renal disease, or other comorbidities with prognoses of less than 12 months.

The study was approved by the ethical committee of Shanghai Chest Hospital. Written informed consent was obtained from all the study participants. All procedures were conducted according to the principles laid down in the World Medical Association's

Declaration of Helsinki. The study was registered at www.clinicaltrials.gov (unique identifier: NCT03252665).

2.2. Study protocol

This study was a prospective, single-blinded, randomized controlled trial. The eligible patients were randomly assigned to the nicorandil, alprostadil, and nitroglycerin groups in a 1:1:1 ratio using random computer-generated numbers. All patients were treated with standard therapeutic regimens according to the current guidelines.^[11] PCI was performed by the same operation team for all groups. A standard angiogram recorded at 15 frames per second was performed via a 6-Fr guiding catheter immediately after a stent was implanted for the assessment of myocardial perfusion. Afterward, in the nicorandil group, 2 mg of nicorandil (Beijing Sihuan Kebao Pharmaceutical Co., Ltd., Beijing, China) dissolved in 3.5 mL of 0.9% saline was administered manually via intracoronary infusion with a targeted perfusion microcatheter (LPRX139, Lepu Medical Technology Co., Ltd., Beijing, China) for 1 minute. In this way, the drug could advance directly to the distal part of the angioplasty site.^[12] Similarly, patients in the alprostadil group received 2 µg of alprostadil (Beijing Tide Pharmaceutical Co., Ltd., Beijing, China) dissolved in 4 mL of 0.9% saline, and those in the nitroglycerin group received 200 µg of nitroglycerin dissolved in 4 mL of 0.9% saline. A repeat angiogram was performed 1 minute after drug infusion.

Loading doses of 300 mg of aspirin and 300 mg of clopidogrel were administered to all patients before PCI unless contraindicated. Consequently, weight-adjusted unfractionated heparin (70–100 U/kg) was administered during the operative procedure to maintain an activated clotting time of more than 250 seconds. Aspirin (100 mg daily) and clopidogrel (75 mg daily) were routinely administered after PCI. Other medications including statins, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), β-blockers, and calcium antagonists were administered at the discretion of the treating physicians.

Blood samples for high-sensitive cTnI were collected at baseline and within 24 hours after PCI using a chemiluminescent immunoassay method (Beckman Coulter ACCESS AccuTnI+3 analyzer; Beckman Coulter, Brea, California, USA). The normal reference value of cTnI was 0.03 ng/mL.

2.3. Endpoints

The primary endpoint was the TIMI myocardial perfusion frame count (TMPFC), a quantitative index for the assessment of myocardial perfusion modified from TIMI myocardial perfusion grade (TMPG).^[13] A right anterior oblique projection with essential caudal angulations was adopted for the left anterior descending artery and left circumflex artery, and a posterior-anterior oblique projection with steep cranial angulations was

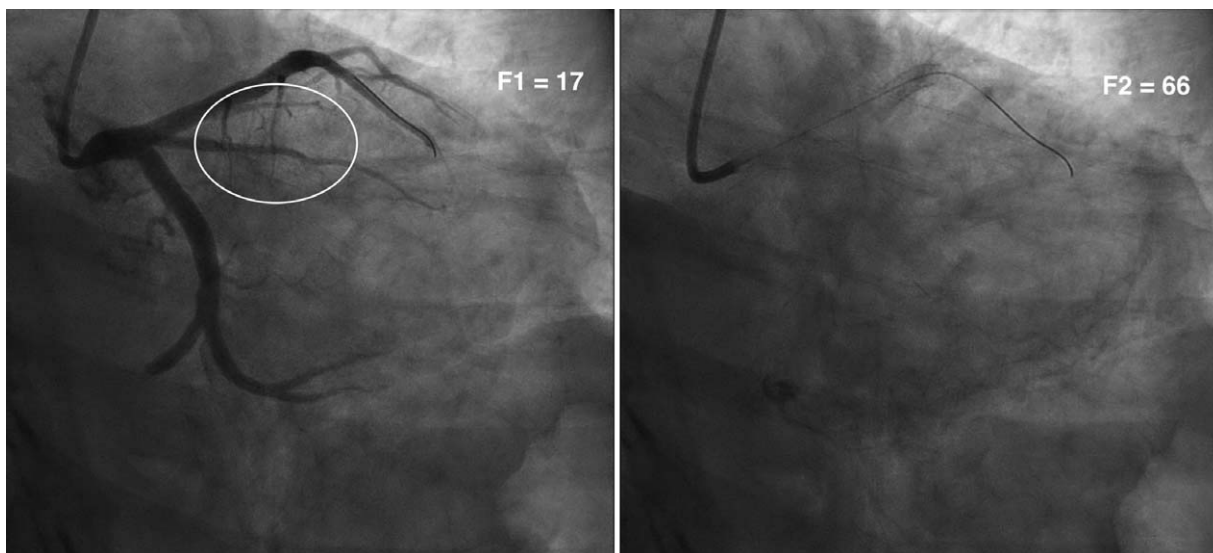


Figure 1. The time course of TMPFC for myocardial perfusion in a patient after successful revascularization of the left anterior descending artery. The opacification of the myocardium occurred at the 17th frame. This frame was thus taken as the first frame of TMPFC (F1). The last frame of TMPFC was the 66th frame, where the contrast was washed out (F2). TMPFC was therefore $(F2 - F1) \times 2 = (66 - 17) \times 2 = 98$ frames, which indicates the myocardial perfusion time for this artery. TMPFC, thrombolysis in myocardial infarction myocardial perfusion frame count.

selected for the right coronary artery. According to our previous study, the first frame of TMPFC was the frame that clearly demonstrated the first appearance of myocardial blush beyond the treated artery (F1), and the last frame was the frame where the contrast was washed out (F2). Thus, TMPFC was $(F2 - F1) \times 2$ frame counts at a filming rate of 15 frames per second (Figs. 1 and 2).^[14]

The secondary endpoints were as follows: i) corrected TIMI frame count (cTFC) and TMPG according to their original definitions^[15] and ii) the occurrence of PMI defined as an elevation of cTnI threshold to 5 times the 99th percentile upper

reference limit (URL) within 24 hours after the operative procedure.^[16]

The TMPFC, cTFC, and TMPG were assessed independently by 2 experienced interventional cardiologists.

2.4. Safety evaluation

Systolic blood pressure, diastolic blood pressure, and heart rate were recorded at baseline and within 5 minutes of administration of the drug. Malignant arrhythmia and heart function were also assessed during the procedure.

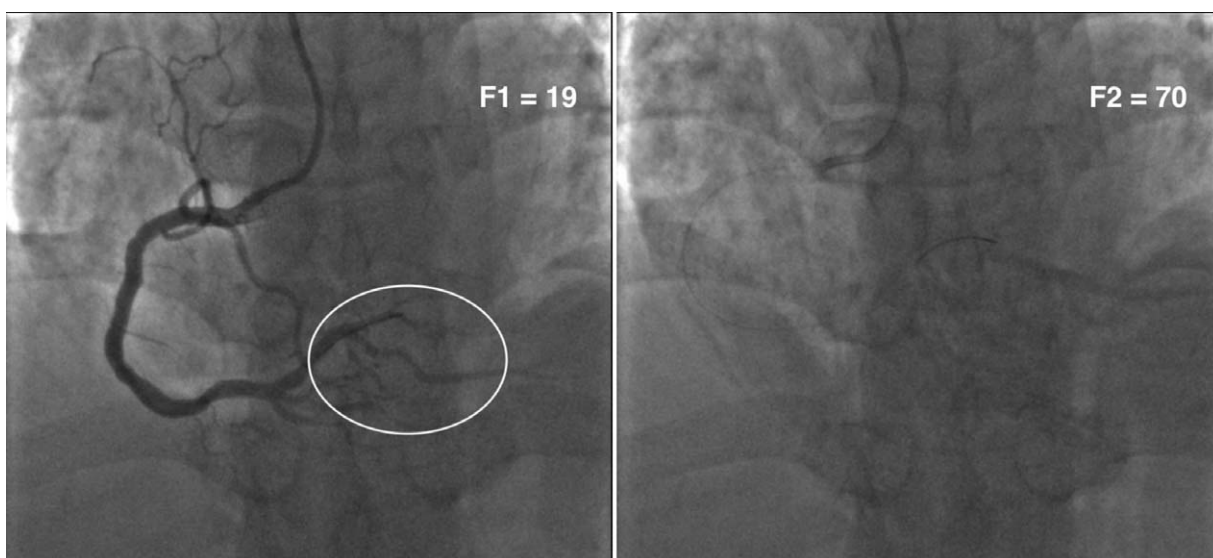


Figure 2. The time course of TMPFC for myocardial perfusion in a patient after successful revascularization of the right coronary artery. The opacification of the myocardium occurred at the 19th frame. This frame was thus taken as the first frame of TMPFC (F1). The last frame of TMPFC was the 70th frame, where the contrast was washed out (F2). TMPFC was therefore $(F2 - F1) \times 2 = (70 - 19) \times 2 = 102$ frames, which indicates the myocardial perfusion time for this artery. TMPFC, thrombolysis in myocardial infarction myocardial perfusion frame count.

2.5. Statistical analysis

According to our pilot data, an average TMPFC value of 118.6 ± 30.5 was found in patients undergoing elective PCI. We assumed a 15% decrease in the TMPFC in the nicorandil and alprostadil groups. It was anticipated that a minimum of 30 patients in each group would be required, basing on the one-sided test with an error limit of 5%, power of 90%, and a dropout rate of 10%.

Continuous variables were expressed as means with standard deviation for normally distributed variables, or as median with interquartile range for non-normally distributed variables. Categorical variables were presented as numbers and percentages (%). Continuous variables were compared among the 3 groups using the one-way analysis of variance for normally distributed values, and the Mann–Whitney *U* test for non-normally distributed values. Chi-square test was used to compare the proportions, and Fisher exact test was used if the expected frequency was less than 5. Paired *t*-tests were conducted to analyze the serial changes in myocardial perfusion and hemodynamic status after the infusion of the drugs in each group. $P < .05$ was considered statistically significant. All analyses were performed using Statistical Package for the Social Sciences, version 23.0 (IBM Corp., Chicago, Illinois, USA).

3. Results

3.1. Baseline characteristics

A total of 90 patients were enrolled in this study. Among them, only 1 patient in the nicorandil group was excluded because of unsatisfied angiogram quality. Therefore, 89 patients (29 in the nicorandil group, 30 in the alprostadil group, and 30 in the nitroglycerin group) were included in the final analysis.

The baseline characteristics of all patients are shown in Table 1. No significant difference was observed in age, gender, proportions of hypertension and diabetes mellitus, and levels of low-density lipoprotein, serum creatine, and left ventricular ejection fraction among the 3 groups. Based on coronary angiography findings, TMPFC, cTFC, TMPG, blood pressure, and heart rate showed no significant difference before the drug infusion.

3.2. Efficacy of nicorandil, alprostadil, and nitroglycerin in ameliorating myocardial perfusion

The TMPFC, as the primary endpoint in this study, was significantly improved after the intracoronary administration of nicorandil (114.6 ± 33.7 vs 93.4 ± 30.9 , $P = .016$) and alprostadil (114.3 ± 34.3 vs 94.7 ± 33.3 , $P = .029$). However, no significant

Table 1
Clinical characteristics and coronary angiographic findings.

Characteristic	Nicorandil (n=29)	Alprostadil (n=30)	Nitroglycerin (n=30)	P value	All patients (n=89)
Age (yr)	67.9 ± 11.9	64.2 ± 9.4	63.8 ± 9.1	.237	65.3 ± 10.2
Age over 75 yr, n (%)	6 (20.7%)	4 (13.3%)	4 (13.3%)	.714	14 (15.7%)
Male, n (%)	18 (62.1%)	22 (73.3%)	21 (70.0%)	.624	61 (68.5%)
Current smoking, n (%)	11 (37.9%)	10 (33.3%)	10 (33.3%)	.913	31 (34.8%)
Hypertension, n (%)	20 (69.0%)	19 (63.3%)	22 (73.3%)	.705	61 (68.5%)
Diabetes mellitus, n (%)	5 (17.2%)	5 (16.7%)	8 (26.7%)	.558	18 (20.2%)
LDL (mmol/L)	2.7 ± 0.8	2.8 ± 0.9	3.2 ± 1.0	.075	2.9 ± 1.0
Serum creatine (μmol/L)	78.6 ± 20.5	76.0 ± 26.1	71.5 ± 13.4	.416	75.3 ± 20.7
LVEF (%)	63.8 ± 2.9	63.5 ± 6.0	62.6 ± 7.3	.728	63.3 ± 5.6
Culprit vessel				.872	
LAD, n (%)	19 (65.5%)	18 (60.0%)	18 (60.0%)		55 (61.8%)
LCX, n (%)	2 (6.9%)	2 (6.7%)	4 (13.3%)		8 (9.0%)
RCA, n (%)	8 (27.6%)	10 (33.3%)	8 (26.7%)		26 (29.2%)
TMPFC pre-perfusion (frames)	114.6 ± 33.7	114.3 ± 34.3	114.4 ± 30.9	.999	114.4 ± 31.0
TMPG pre-perfusion				.937	
Grade 2, n (%)	5 (17.2%)	5 (16.7%)	4 (13.3%)		14 (15.7%)
Grade 3, n (%)	24 (82.8%)	25 (83.3%)	26 (86.7%)		75 (84.3%)
cTFC pre-perfusion (frames)	20.3 ± 10.5	20.2 ± 7.4	19.4 ± 7.2	.907	19.7 ± 8.3
SBP pre-perfusion (mmHg)	136.2 ± 25.5	130.8 ± 20.7	130.4 ± 20.7	.541	132.4 ± 22.3
DBP pre-perfusion (mmHg)	72.7 ± 11.6	73.1 ± 10.9	74.4 ± 10.3	.828	73.4 ± 10.8
HR pre-perfusion (bpm)	73.0 ± 10.2	72.0 ± 10.0	71.0 ± 9.9	.747	72.0 ± 10.0
TMPFC post-perfusion (frames)	93.4 ± 30.9	94.7 ± 33.3	112.1 ± 31.9	.048*	100.1 ± 32.8
TMPG post-perfusion				.122	
Grade 2, n (%)	0 (0%)	1 (3.3%)	4 (13.3%)		5 (5.6%)
Grade 3, n (%)	29 (100%)	29 (96.7%)	26 (86.7%)		84 (94.4%)
cTFC post-perfusion (frames)	13.5 ± 5.0	15.2 ± 5.2	19.3 ± 7.2	.001**	16.0 ± 6.3
SBP post-perfusion (mmHg)	133.7 ± 24.5	128.2 ± 22.1	113.6 ± 19.0	.002**	125.2 ± 23.3
DBP post-perfusion (mmHg)	70.8 ± 11.2	70.1 ± 10.1	68.5 ± 11.0	.715	69.8 ± 10.7
HR post-perfusion (bpm)	72.6 ± 10.7	72.8 ± 9.7	72.9 ± 9.3	.993	72.8 ± 9.8
Change of TMPFC (frames)	21.2 ± 22.8	19.6 ± 16.3	2.3 ± 26.8	.003**	14.3 ± 23.7
Change of cTFC (frames)	6.8 ± 7.9	5.0 ± 5.5	0.1 ± 7.5	.001**	4.0 ± 7.5

cTFC = corrected thrombolysis in myocardial infarction frame count, DBP = diastolic blood pressure, HR = heart rate, LAD = left anterior descending branch, LCX = left circumflex branch, LDL = low-density lipoprotein, LVEF = left ventricular ejection fraction, RCA = right coronary artery, SBP = systolic blood pressure, TMPFC = thrombolysis in myocardial infarction myocardial perfusion frame count, TMPG = thrombolysis in myocardial infarction myocardial perfusion grade.

* $P < .05$; ** $P < .01$.

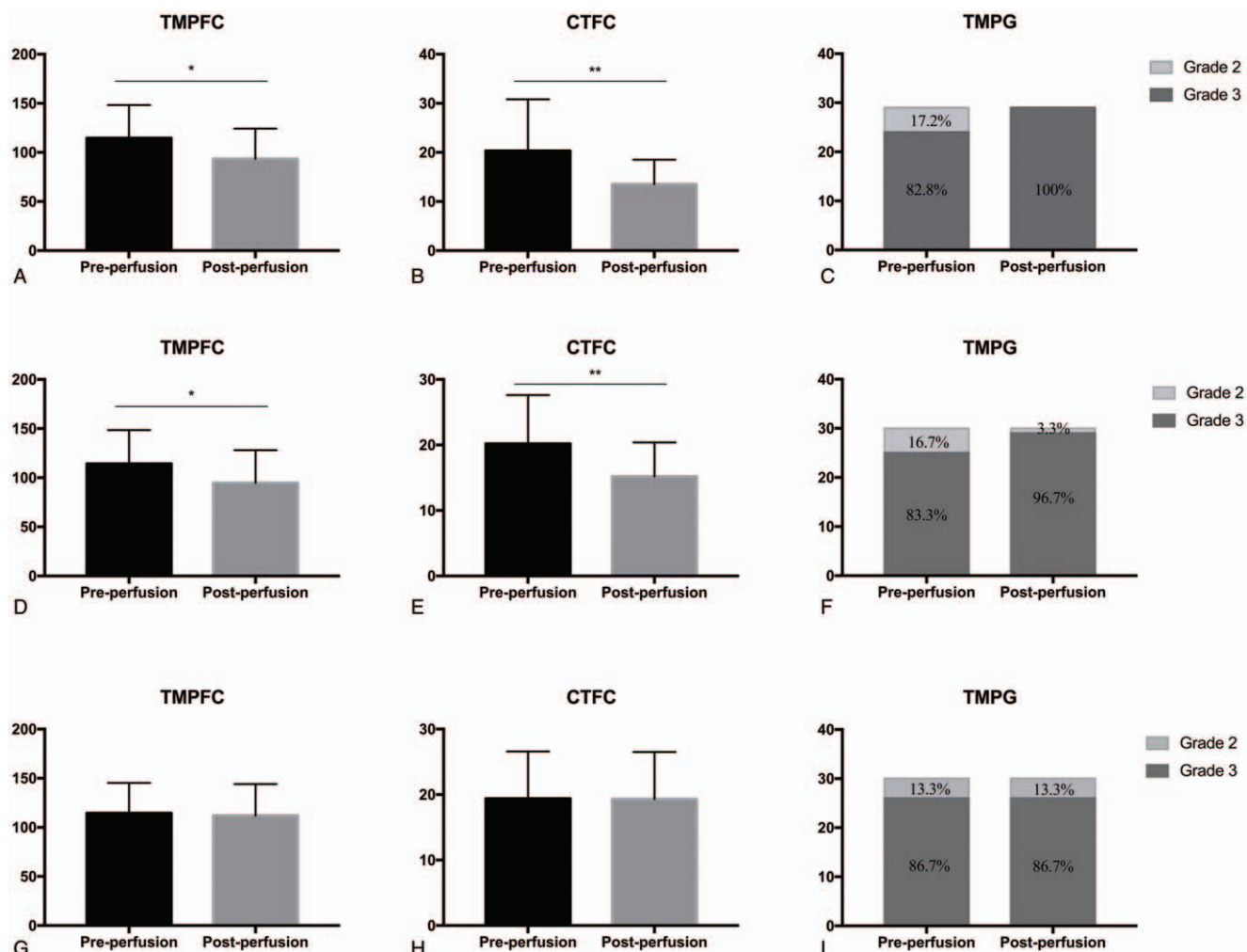


Figure 3. Efficacy of nicorandil, alprostadil, and nitroglycerin in ameliorating myocardial perfusion. (A) to (C): TMPFC, cTFC, and TMPG in the nicorandil group; (D) to (F): TMPFC, cTFC, and TMPG in the alprostadil group; (G) to (I): TMPFC, cTFC, and TMPG in the nitroglycerin group. TMPFC, thrombolysis in myocardial infarction myocardial perfusion frame count; cTFC, corrected thrombolysis in myocardial infarction frame count; TMPG, thrombolysis in myocardial infarction myocardial perfusion grade. * $P < .05$; ** $P < .01$.

change was found in the TMPFC (114.4 ± 30.9 vs 112.1 ± 31.9 , $P = .739$) after the infusion of the drug in the nitroglycerin group (Table 1 and Fig. 3A, 3D, and 3G).

cTFC was also observed to be decreased in the nicorandil (20.3 ± 10.5 vs 13.5 ± 5.0 , $P = .003$) and alprostadil (20.2 ± 7.4 vs 15.2 ± 5.2 , $P = .003$) groups after the injection of drug, with a limited change observed in the nitroglycerin group (19.4 ± 7.2 vs 19.3 ± 7.2 , $P = .936$) (Table 1 and Fig. 3B, 3E, and 3H).

An upward trend was observed in the percentages of TMPG 3 after the administration of nicorandil (100% vs 82.8%, $P = .052$) and alprostadil (83.3% vs 96.7%, $P = .196$), though without statistical difference. The distribution of TMPG remained unchanged in the nitroglycerin group (86.7% vs 86.7%, $P = 1.000$) (Table 1 and Fig. 3C, 3F, and 3I).

3.3. Comparative effect on myocardial protection among the 3 groups

A significant difference was found in the TMPFC among the 3 groups after infusion of drug (Δ TMPFC: 21.2 ± 22.8 vs 19.6 ± 16.3 vs 2.3 ± 26.8 , $P = .003$) (Table 1). Post hoc analysis

suggested that the change value in the TMPFC was statistically different between the nicorandil and nitroglycerin groups ($P = .002$), and between the alprostadil and nitroglycerin groups ($P = .004$). However, no difference was observed between the nicorandil and alprostadil groups ($P = .779$) (Table 2).

In addition, similar findings were observed in the improvement of cTFC (Δ cTFC: 6.8 ± 7.9 vs 5.0 ± 5.5 vs 0.1 ± 7.5 , $P = .001$) (Table 1). The change value was statistically different between the nicorandil and nitroglycerin groups ($P = .000$), and between the alprostadil and nitroglycerin groups ($P = .008$). Likewise, no difference was found between the nicorandil and alprostadil groups ($P = .333$) (Table 2).

3.4. Impact on the incidence of PMI

Postoperative assessment of cTnI was available for 78 patients in this study. PMI occurred in 16.7% (4/24) of the patients in the nicorandil group, 16.0% (4/25) in the alprostadil group, and 27.6% (8/29) in the nitroglycerin group. No significant difference was found among the 3 groups ($P = .537$), though the occurrence

Table 2
Post hoc analysis of the change of thrombolysis in myocardial infarction myocardial perfusion frame count and corrected thrombolysis in myocardial infarction frame count among 3 groups.

Characteristic	Group	Mean difference	95% Confidential interval	P value	
Change of TMPFC	Nicorandil	Alprostadil	1.6	-10.0 to 13.2	.779
		Nitroglycerin	18.8	7.1 to 30.3	.002**
	Alprostadil	Nicorandil	-1.6	-13.2 to 10.0	.779
		Nitroglycerin	17.3	5.6 to 28.6	.004**
	Nitroglycerin	Nicorandil	-18.8	-30.3 to -7.1	.002**
		Alprostadil	-17.3	-28.6 to -5.6	.004**
Change of cTFC	Nicorandil	Alprostadil	1.8	-1.9 to 5.4	.333
		Nitroglycerin	6.7	3.1 to 10.3	.000**
	Alprostadil	Nicorandil	-1.8	-5.4 to 1.9	.333
		Nitroglycerin	4.9	1.3 to 8.5	.008**
	Nitroglycerin	Nicorandil	-6.7	-10.3 to -3.1	.000**
		Alprostadil	-4.9	-8.5 to -1.3	.008**

cTFC=corrected thrombolysis in myocardial infarction frame count, TMPFC=thrombolysis in myocardial infarction myocardial perfusion frame count.

** $P < .01$.

of PMI was comparatively lower in the nicorandil and alprostadil groups.

3.5. Safety of intracoronary drug infusion

The intracoronary administration of nitroglycerin resulted in a significant drop in both systolic blood pressure and diastolic blood pressure (130.4 ± 20.7 vs 113.6 ± 19.0 , $P = .002$; 74.4 ± 10.3 vs 68.5 ± 11.0 , $P = .039$, respectively). In contrast, blood pressure mildly changed after the intracoronary injection of nicorandil and alprostadil, with sustained heart rate (Table 1). Furthermore, neither malignant arrhythmias nor hemodynamic instability was observed during the procedure.

4. Discussion

To the best of our knowledge, this is the first study elucidating the beneficial effects of nicorandil and alprostadil on myocardial perfusion in patients with non-ACS undergoing elective PCI. Our data demonstrated that the intracoronary administration of nicorandil and alprostadil via a targeted perfusion microcatheter obtained significant improvement in TMPFC and cTFC, both superior to nitroglycerin. Furthermore, amelioration of myocardial perfusion was accompanied by a moderate decrease in the incidence of PMI, suggesting that intraoperative administration of nicorandil and alprostadil could be a useful step for myocardial protection during elective PCI.

Strategies have been made to improve myocardial perfusion after PCI. Studies and meta-analyses indicate that verapamil, an L-type calcium channel blocker, can improve microvascular dysfunction by releasing microvascular spasm and regulating endothelial function.^[17] However, the development of transient atrioventricular block or a significant drop in blood pressure was observed after intracoronary injection of verapamil.^[18] In addition, other medications such as sodium nitroprusside, diltiazem, and adenosine also restrict clinical use due to various side effects including hypotension, bradycardia, and bronchospasm, though they are shown to be effective in ameliorating myocardial perfusion.^[19] Nicardipine, a dihydropyridine calcium-channel blocker with endothelium-independent vasodilatory effects, is also proved to be a potential therapeutic approach in reversing no-reflow during PCI and spontaneous coronary slow-flow phenomenon without significant adverse hemodynamic or

chronotropic effects.^[20,21] Meanwhile, the disparity in the optimal dosage might cause uncertainty in its clinical use.

Nicorandil is an ATP-sensitive K^+ ATP open agent with the effect of nitrate. Its action on nitrate-mediated channels causes vasodilation of the systemic vessels and coronary arteries, while the opening of K^+ ATP potassium channels induces alleviation of coronary arterioles resistance and spasm.^[22,23] The intracoronary and intravenous administration of nicorandil have been proved efficient in resolving no-reflow or slow-flow phenomenon in primary PCI.^[6-9] This study suggested that nicorandil also played an effective role in elective settings. Based on TMPFC,^[13,14] a quantitative index for blush duration that proved to be associated with microvascular function and clinical outcomes, we found an approximately 18% improvement in myocardial perfusion after the intracoronary administration of nicorandil via a targeted perfusion microcatheter. Similar findings were observed in cTFC assessment, indicating the beneficial effect of nicorandil in both myocardial and epicardial levels. Meanwhile, the intracoronary use of alprostadil was also found effective in ameliorating myocardial and epicardial perfusion. The beneficial effect of alprostadil might be attributed to its pharmacological effects, including inhibition of platelet aggregation, dilation of coronary arterioles, and prevention of ischemia-reperfusion injury.^[24] Alternatively, the intracoronary administration of nitroglycerin produced little effect on myocardial and epicardial perfusion, as limited changes were observed in TMPFC and cTFC after drug infusion. One explanation for this phenomenon might be due to the vasodilating effect of nitroglycerin, which primarily affects large coronary vessels instead of arterioles. Another reason that nitroglycerin was not an ideal drug for myocardial protection might be its indirect action on coronary smooth muscle. Unlike nicorandil or alprostadil, it has to be converted into vasoactive metabolites before taking effect.^[25] This would explain the refractory response to nitroglycerin in attempts to address the no-reflow or slow-flow phenomenon, especially in the setting of ischemia with impaired ability of microvasculature in metabolizing nitrates.^[26,27] In addition, we compared the myocardial protective effects of nicorandil, alprostadil, and nitroglycerin in this study. It was found that the intracoronary administration of nicorandil and alprostadil led to a similar reduction in TMPFC and cTFC, which indicated their identical efficacy in improving myocardial and epicardial perfusion, both superior to

nitroglycerin. Furthermore, the intracoronary injection of nicorandil and alprostadil produced mild effects on blood pressure and heart rate, without malignant arrhythmias and hemodynamic instability observed. Apart from the pharmacodynamic effects of the drugs, another important reason might be the targeted perfusion microcatheter used for drug administration in this study. A targeted perfusion microcatheter could reach the distal part of the angioplasty site through a guidewire, and drugs could be released directly into the target artery. It allowed a relatively high concentration in the local coronary area with limited systemic adverse consequences, which ensured a positive effect on myocardial protection but mild influence on the hemodynamic status.^[10]

Traditionally, a normal microvascular perfusion was determined using TMPG if myocardial blush in the distribution of culprit vessel is gone or diminished after 3 cycles of cardiac phase, according to its original definition.^[15] It is useful in the evaluation of post-reperfusion myocardial patency and the prediction of adverse clinical outcomes in patients with STEMI.^[28–31] However, the semiquantitative and discontinuous criterion of TMPG restricts its sensitivity and accuracy in the detection of minor changes in myocardial perfusion, which could be reflected by the upward but not statistically different change in the percentage of TMPG 3 after the administration of nicorandil and alprostadil. Thus, TMPFC was a preferred and more sensitive index in the assessment of microvascular status. It explained the reason why we adopted TMPFC as the primary endpoint in this study.

PMI, a frequent complication of elective PCI, is associated with longer hospital stay and worse short- and long-term prognoses.^[32] The pathophysiology of PMI is complex and multifactorial. It can be classified into 2 types: i) type 1, also named proximal type, is most often seen adjacent to the treated arterial segment, mainly attributed to procedure-related complications such as side-branch occlusion or dissection and ii) type 2, also called distal type, is seen in the distal perfusion territory of the treated epicardial artery due to microvascular obstruction. The potential mechanisms may include thrombus microembolization, coronary microvascular spasm, and oxidative stress.^[3] In this study, we adopted the acknowledged definition of PMI as an elevation of cTnI threshold to 5 times the 99th percentile URL according to the fourth universal definition of myocardial infarction.^[16,33] No significant difference in the incidence of PMI was found among the patients in the nicorandil, alprostadil, and nitroglycerin groups. This was partly consistent with the results of previous studies, which claimed that nicorandil had a negative effect on PMI.^[34–38] Note that a moderate decrease in the incidence of PMI was detected after the intracoronary administration of nicorandil and alprostadil via a targeted perfusion microcatheter, which differed sharply in the way of drug administration from those studies. Since this trial was not primarily designed to determine the comparative efficacy of these drugs on PMI, future studies are encouraged to elucidate the cardiac protective effect of intracoronary nicorandil and alprostadil from this perspective.

Last but not least, our findings obtained in elective settings might also provide a potential approach in the management of STEMI. Over the past years, national door-to-balloon times have improved significantly in patients undergoing primary PCI. Unfortunately, in-hospital mortality has remained substantially unchanged.^[39] One important reason for this is the occurrence of coronary microvascular dysfunction,^[40] which affects approximately 50% of patients with STEMI and is associated

with adverse outcomes, despite timely and successful restoration of epicardial infarct-related artery patency.^[41,42] Therefore, an integrated therapeutic method targeting effective myocardial as well as epicardial reperfusion may help to improve the clinical prognosis.^[43] In agreement with this point of view, the intracoronary administration of nicorandil or alprostadil could be a cardioprotective strategy for the optimal treatment of STEMI following primary PCI.

4.1. Study limitations

We acknowledge several limitations to this study. First, this was a single-blinded and relatively small-scale study conducted at a single center. The study results can be validated with a larger sample of patients from multiple centers. Second, since the index of microcirculatory resistance was not measured in this study, the myocardial perfusion status from a functional aspect could not be assessed. Third, due to limited imaging tests such as single-photon emission computed tomography or cardiac magnetic resonance imaging performed, the precise degree of myocardial injury following PCI could not be determined. Fourthly, the targeted perfusion microcatheter was used in this study to ensure the direct release of drugs into the target artery with minimal systemic side effects. However, we knew that it would increase the total cost and have potential for harm of the vessels given exchanges along with prolonged time and radiation exposure. Last but not least, we expected a low rate of clinical events in these clinically stable patients and therefore chose the surrogate instead of hard endpoints. Future studies are needed to explore the effect of nicorandil and alprostadil on long-term outcomes, or translate these data to the ACS cohort to further improve their clinical prognosis.

5. Conclusion

The intracoronary administration of nicorandil and alprostadil via a targeted perfusion microcatheter was effective in improving myocardial perfusion in patients undergoing elective PCI, both superior to nitroglycerin.

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