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*Original Article*

# Acute effects of intracoronary nicorandil and nitroglycerin in patients with coronary slow flow

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**Abstract:** *Objective:* This study aimed to assess the acute effects of intracoronary nicorandil and nitroglycerin in patients with coronary slow flow (CSF). *Methods:* Totally, 60 patients with CSF were enrolled in this retrospective study and divided into nicorandil group (n = 30) and nitroglycerin group (n = 30). Coronary angiography was administered to intracoronary nitroglycerin or nicorandil 30 seconds later. The coronary blood flow of patients was evaluated by thrombolysis in myocardial infarction (TIMI) frame count (TFC) method. Heart rate, systolic and diastolic blood pressures, and TFCs in left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) were recorded before and after administration with nicorandil or nitroglycerin. *Results:* After nitroglycerin administration, systolic and diastolic blood pressures decreased, heart rates significantly increased ($P < 0.001$). However, systolic and diastolic blood pressures, heart rate had no significant changes after the application of intracoronary nicorandil. In addition, after administration with nicorandil or nitroglycerin, TFCs in LAD, LCX, and RCA were significantly decreased ($P < 0.001$) compared with before administration; however, TFCs recovered to the normal level in the nicorandil group but not nitroglycerin group. We also found that the percentages reduction of TFCs in all coronaries were higher in the nicorandil group than that in the nitroglycerin group ($P < 0.001$). Coronary angiogram further showed that both nicorandil and nitroglycerin improved the coronary flow, while nicorandil had better improvement effect than nitroglycerin. *Conclusions:* The acute effect of intracoronary nicorandil is superior to nitroglycerin in ameliorating CSF.

**Keywords:** Coronary slow flow, intracoronary nicorandil/nitroglycerin, thrombolysis in myocardial infarction frame count, coronary angiogra

## Introduction

The phenomenon of coronary slow flow (CSF) is not a rare angiographic finding, characterized by delayed progression of contrast medium into distal coronary artery without obvious obstructive lesion stenosis in epicardial coronary artery [1, 2]. The patients with CSF are usually associated with clinical manifestations of a long period of chest pain or acute coronary syndrome such as arrhythmias, myocardial ischemia, sudden cardiac death [3, 4]. However, little attention has been focused on the CSF and the pathophysiological mechanism of this phenomenon is still unclear.

Currently, several studies have proposed that CSF may be related to endothelial cell dysfunction, microangiopathy, inflammation, atherosclerosis, platelet dysfunction, and microvascular spasm [5-7]. Hereinto, microangiopathy is considered as the most important reason for the formation of CSF [8]. Therefore, some clinical drugs, which used to improve microvascular function, are often applied in the treatment of CSF. Previous study has shown that intracoronary administration of nitroglycerin may not be effective to normalize the flow, especially in patients with CSF who have angina symptom [9, 10]. Exhilaratingly, nicorandil, a potassium channel opener, is a novel anti-angina medication and has a significant vasodilatory effect on small and large coronary arteries [11], which prompts that nicorandil may be a choice for the treatment of patients with CSF. Recently, Sani *et al.* [12] have compared the efficacies of oral

nicorandil versus nitroglycerin for alleviating angina in patients with CSF. However, few studies have compared the acute effects of nicorandil and nitroglycerin on the coronary flow improvement in patients with CSF. Therefore, the present study compared the effects of the intracoronary administration of nicorandil versus nitroglycerin during coronary angiography on blood pressure, heart rate and thrombolysis in myocardial infarction (TIMI) frame counts (TFC) in patients with CSF.

## Materials and methods

### *Patients*

Between November 2013 and December 2014, a total of 4,300 patients with suspicious myocardial ischemia performed coronary angiography at the affiliated hospital of Qingdao university. The patients who diagnosed with CSF during angiography were included in this retrospective study. The CSF was diagnosed according to TFCs method described by Gibson *et al*. [13]. Briefly, using an acquisition speed of 30 frames per second, the number of frames was calculated from the first frame to the last frame. The first frame was confirmed when contrast media filled the origin of coronary artery, touched both sides of the vessel wall, and moved in an anterograde manner. The last frame was identified when contrast media arrived at the distal landmark branch of coronary artery. Due to the greater length of left anterior descending artery (LAD) than left circumflex artery (LCX) and right coronary artery (RCA), the frame count of LAD should be divided by 1.7 to obtain the corrected TFC (CTFC). The CSF was defined as a CTFC > 27 in at least one vessel [14]. The exclusion criteria were: (1) during coronary angiography, no-reflow phenomenon, arterial narrowing > 50%, coronary artery dilatation, or coronary artery spasm were observed in patients; (2) patients had histories of myocardial infarction and coronary artery intervention; (3) patients had cardiomyopathy, heart valve disease, hypertensive heart disease, connective tissue diseases, congenital heart disease, or left ventricular ejection fraction < 50%; and (4) patients were vulnerable to nitroglycerin and nicorandil. As a result, a total of 60 patients with CSF were enrolled in our study. Approval from the Ethics Committee of the affiliated hospital of Qingdao university was obtained.

### *Study design*

Totally, 60 eligible patients with CSF were divided into two groups according to the therapeutic medication: nicorandil group (n = 30, 22 males and 8 females, average age of 59.3 ± 11.5 years) and nitroglycerin group (n = 30, 19 males and 11 females, average age of 56.7 ± 11.2 years). The baseline characteristics, including age, sex, diabetes, hypertension, blood lipid, body mass index (BMI), and adjuvant drugs were recorded. In addition, treadmill exercise testing (TET) was performed.

### *Treatment method*

Selective coronary angiography was carried out using Allura Xper FD20 (Philips, Amsterdam, Netherlands) by Judkins' technique. Patients laid in the horizontal supine position and accepted regional anesthesia. Next, patients performed radial artery or femoral artery puncture, then the 6F angiography catheter was placed into the aortic root via puncture site. Contrast media was injected when catheter was adjusted into left or right coronary opening. Meanwhile, continuous X-ray photography was carried out at the appropriate section. During angiography, patients with CSF in the nicorandil group were administrated with nicorandil (Sihuan Kebao pharmaceutical Co., LTD, Beijing, China) via coronary into the left (150 μg) or right (100 μg) coronary artery by a bolus-like injection. Nitroglycerin (Sihuan Kebao pharmaceutical Co., LTD, Beijing, China) was administered via coronary to the left (1.5 mg) or right (1 mg) coronary artery for the patients in the nitroglycerin group.

### *Assessment*

Blood pressure and heart rate were recorded before and after treatment for 30 seconds. In addition, the distribution and the number of artery with CSF were calculated. TFC of each branch of coronary artery or CTFC were recorded pre- and post-administration. The percentage reduction of TFCs was measured as $(TFC_{\text{before administration}} - TFC_{\text{after administration}})/TFC_{\text{before treatment}} \times 100\%$.

### *Statistical analysis*

Data analysis was performed by using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

**Table 1.** Baseline characteristics of the patients in the nitroglycerin and nicorandil groups

| Index | Nitroglycerin group (n = 30) | Nicorandil group (n = 30) | *P* |
|---|---|---|---|
| Age (year) | 58.7 ± 10.6 | 59.3 ± 11.5 | 0.825 |
| Male/female | 21/9 | 22/8 | 0.774 |
| Diabetes (%) | 5 (16.7) | 6 (20.0) | 0.739 |
| Hypertension (%) | 17 (56.7) | 19 (63.3) | 0.598 |
| BMI (kg/m$^2$) | 27.3 ± 4.2 | 26.8 ± 4.0 | 0.635 |
| Adjuvant drugs (%) | | | |
| β-blockers | 9 (30.0) | 11 (36.6) | 0.584 |
| Statins | 9 (30.0) | 8 (26.7) | 0.774 |
| ARB | 6 (13.3) | 5 (16.7) | 0.739 |
| ACEI | 7 (23.3) | 9 (30.0) | 0.559 |
| HDL-c (mmol/L) | 1.3 ± 0.2 | 1.3 ± 0.3 | 0.695 |
| LDL-c (mmol/L) | 2.5 ± 0.5 | 2.6 ± 0.5 | 0.799 |
| Positive TET (%) | 6 (20.0) | 7 (23.3) | 0.754 |

BMI, body mass index; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitors; HDL-c, high-density lipoproteincholesterol; LDL-c, low-density lipoproteincholesterol; TET, treadmill exercise testing.

**Table 2.** The distribution and the number of artery with CSF in the nitroglycerin and nicorandil groups

| Index | Nitroglycerin group (n = 30) | Nicorandil group (n = 30) | *P* |
|---|---|---|---|
| LAD (%) | 27 (90) | 26 (87) | 0.688 |
| LCX (%) | 20 (74) | 19 (63) | 0.787 |
| RCA (%) | 14 (47) | 15 (50) | 0.606 |
| The average number of artery with CSF | 2.03 ± 0.76 | 2.07 ± 0.64 | 0.855 |

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CSF, coronary slow flow.

Continuous and categorical data were expressed as mean value ± SD and percentage (%), respectively. Baseline characteristics as well as the distribution and the number of arteries with CSF between the nicorandil and nitroglycerin groups were compared by paired *t*-test or chi-square test. Blood pressure, heart rate, and TFC or CTFC pre- and post- administration were compared by paired *t*-test. The percentage reduction of TFCs were analyzed by two independent sample *t* test. *P* values of less than 0.05 were considered statistically significant.

## Results

### *Patient characteristics*

The baseline characteristics of the patients are shown in **Table 1**. No significant differences were found between the nicorandil and nitroglycerin groups in baseline characteristics, including age, sex, diabetes, hypertension, blood lipid and BMI, and adjuvant drugs. In addition, there were 6 (20.0%) patients with positive TET in the nitroglycerin group and 7 (23.3%) patients in the nicorandil group, without statistical difference.

Coronary angiography displayed that 60 patients had no obvious stenosis in epicardial coronary artery, while there were different degree of CSF in LAD, left circumflex artery (LCX), and right coronary artery (RCA). CSF existed in 90% LAD, 74% LCX and 47% RCA in the nitroglycerin group, as well as 87% LAD, 63% LCX and 50% RCA in the nicorandil group, without statistical difference between these two groups (**Table 2**). Also, the average number of arteries with CSF in the nitroglycerin group did not show significant difference compared with the nicorandil group (**Table 2**).

### *Outcomes*

Patients had well tolerance of nicorandil or nitroglycerin and no adverse reactions were documented after administration with drugs. In the nitroglycerin group, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were remarkably decreased ($P < 0.001$), while heart rate was significantly increased ($P < 0.001$) after administration compared with before administration (**Table 3**). However, SBP, DBP and heart rate were all similar between pre- and post- administration in the nicorandil group (**Table 3**). Furthermore, there was no significant difference in the baseline TFC between the nicorandil and nitroglycerin groups. After administration with nitroglycerin or nicorandil, CTFC or TFCs in LAD, LCX, and RCA were significantly decreased ($P < 0.001$) compared with before administration; however, CTFC or TFCs

**Table 3.** Blood pressure and heart rate in the nitroglycerin and nicorandil groups before and after treatment (mean ± SD)

| Index | Nitroglycerin group (n = 30) | | | Nicorandil group (n = 30) | | |
|---|---|---|---|---|---|---|
| | Before administration | After administration | *P* | Before administration | After administration | *P* |
| HR (beat/min) | 71.7 ± 12.3 | 82.3 ± 12.1 | < 0.001 | 74.8 ± 11.5 | 74.9 ± 11.8 | 0.872 |
| SBP (mmHg) | 131.1 ± 19.4 | 112.5 ± 17.4 | < 0.001 | 128.8 ± 21.0 | 128.7 ± 21.2 | 0.442 |
| DBP (mmHg) | 82.0 ± 12.2 | 71.4 ± 11.3 | < 0.001 | 76.9 ± 14.5 | 76.7 ± 14.3 | 0.407 |

HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

**Table 4.** The thrombolysis in Myocardial Infarction frame count in the nitroglycerin and nicorandil groups before and after treatment (mean ± SD)

| Index | Nitroglycerin group (n = 30) | | | Nicorandil group (n = 30) | | |
|---|---|---|---|---|---|---|
| | Before administration | After administration | *P* | Before administration | After administration | *P* |
| CLAD | 35.86 ± 6.69 | 27.73 ± 5.39 | < 0.001 | 38.15 ± 6.54 | 17.94 ± 5.24 | < 0.001 |
| LAD | 63.52 ± 13.56 | 47.15 ± 9.16 | < 0.001 | 64.69 ± 11.00 | 30.50 ± 8.91 | < 0.001 |
| LCX | 45.90 ± 14.93 | 32.32 ± 9.93 | < 0.001 | 46.58 ± 13.25 | 26.26 ± 5.40 | < 0.001 |
| RCA | 51.21 ± 13.98 | 34.00 ± 10.27 | < 0.001 | 49.93 ± 14.57 | 25.13 ± 5.30 | < 0.001 |

CLAD, corrected left anterior descending artery; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CSF, coronary slow flow.

**Table 5.** The percentage reduction of the thrombolysis in Myocardial Infarction frame count in the nitroglycerin and nicorandil groups (mean ± SD)

| Index | Nitroglycerin group (n = 30) | Nicorandil group (n = 30) | *P* |
|---|---|---|---|
| LAD (%) | 25.38 ± 7.79 | 51.83 ± 8.02 | < 0.001 |
| LCX (%) | 32.25 ± 9.01 | 41.90 ± 13.00 | 0.010 |
| RCA (%) | 37.02 ± 12.01 | 47.31 ± 8.90 | 0.014 |

LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CSF, coronary slow flow.

recovered to the normal level in the nicorandil group but not nitroglycerin group (**Table 4**). We also found that after administration with nicorandil or nitroglycerin, the percentages reduction of TFCs in LAD, LCX, and RCA were higher in the nicorandil group than that in the nitroglycerin group ($P < 0.001$) (**Table 5**). Coronary angiogram showed that both nicorandil and nitroglycerin improved the coronary flow, while nicorandil had better improvement effect than nitroglycerin (**Figure 1**).

## Discussion

In the present study, we compared the acute effects of nicorandil and nitroglycerin on the coronary flow improvement in patients with CSF. Our results showed that SBP and DBP were remarkably decreased as well as heart rate was significantly increased after administration with nitroglycerin but not nicorandil. Furthermore, although both nicorandil and nitroglycerin could decrease CTFC or TFCs, CTFC or TFCs recovered to the normal level in the nicorandil group and the percentages reduction of TFCs were higher in the nicorandil group than that in the nitroglycerin group. Consistently, coronary angiogram showed that nicorandil had better improvement effect than nitroglycerin.

CSF is a common complication in coronary intervention, and the administration of adenosine [15], diltiazem [16], mibefradil [17] and dipyridamole [18] exerted similar improved effects on patients with CSF. The vasodilatory effects of these agents were speculated as the mechanism of improving CSF. Previous studies had suggested that nitrates could increase TFCs in healthy subjects by dilating epicardial conduit arteries and small coronary resistance arteries [19, 20]. However, the effects of nitrates were conflicting in patients with CSF [21-23]. Some patients showed no change, while others suggested decreased or increased effect on coronary flow after administration

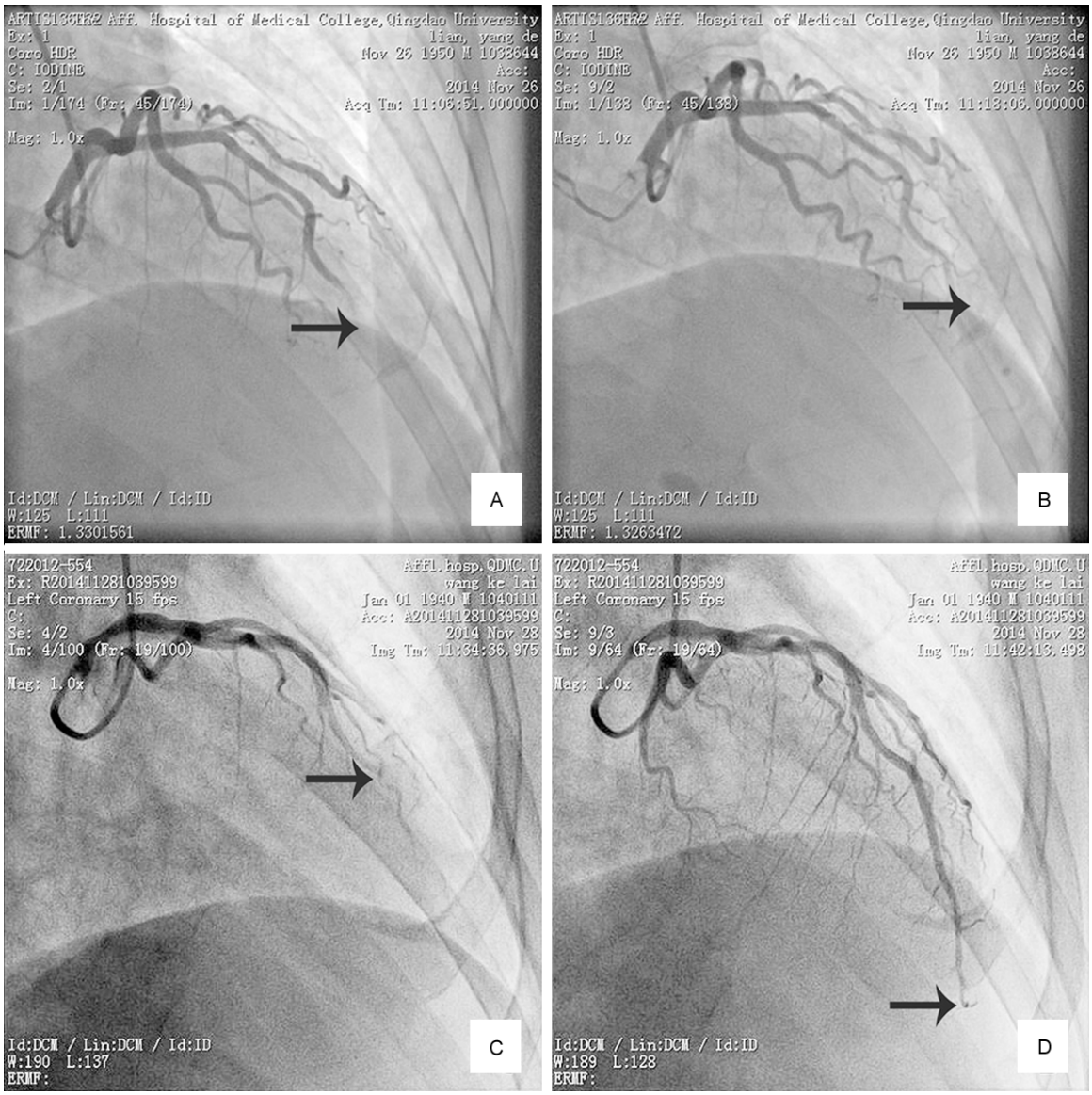


**Figure 1.** Coronary angiograms in the nitroglycerin and nicorandil groups before and after treatment. Coronary angiogram at the 44th frame count of a patient with the coronary slow flow phenomenon, the baseline coronary flow was severely delayed (A), and administration of nitroglycerin improved the flow (B); Coronary angiogram at the 19th frame count of a patient with the coronary slow flow phenomenon, the baseline flow was severely delayed (C), and injection of nicorandil significantly ameliorated the flow (D). The arrows indicate the distal point to which the contrast reached in the left anterior descending artery.

with nitrates. Nitroglycerin had been proved to dilate coronary vessels, while it had unequal effects on the dilation of coronary microvascular. It was suggested that nitroglycerin could dilate coronary vessels with diameter more than 100-200 μm, but had no effect on coronary vessels with diameter less than 100 μm [9]. Ozdogru *et al.* [16] had demonstrated the decreased TFCs in LAD, LCX, and RCA. Similarly, our study also showed that nitroglycerin decreased CTFC or TFCs in all coronaries, while TFCs could not recover to the normal level. This may be caused by the different diameters of the constricted vessels and nitroglycerin had some improvement in CSF.

Compared with nitroglycerin, nicorandil was a compound combined with nicotinamide and organic nitrate and it not only exerted vasodilatory effect on coronary vessels due to nitrate-

like properties, but also dilated coronary microvascular through opening adenosine triphosphate sensitive potassium channel [11]. Our study showed that nicorandil could recover the normal level of TFCs and obtain the higher percentages reduction of TFCs compared with nitroglycerin, suggesting that intracoronary nicorandil is superior to nitroglycerin in reducing TFCs in patients with CSF. Previous studies had shown that intracoronary nicorandil had more effective improvement in myocardial perfusion of patients with acute myocardial infarction as well as epicardial and microvascular spasms than nitrates [24-26]. Consistent with our study, the acute effect of intracoronary nicorandil on reducing TFCs was superior to isosorbide dinitrate in patients with CSF [27]. In addition, we found that compared with nitroglycerin, nicorandil had no obvious effect on blood pressure and heart rate in patients with CSF, indicating a better safety of nicorandil than nitroglycerin. Previous clinical trial demonstrated that oral nicorandil reduced angina frequency and intensity in patients with CSF in comparison with nitroglycerin [12]. Moreover, IONA study group revealed that oral nicorandil but not nitrates could reduce the risk of chest pain, hospitalization incidence, myocardial infarction, and cardiac death in patients with stable angina [28]. Therefore, we speculated that nicorandil might be a promising agent for the treatment of patients with CSF.

Unfortunately, this study has several limitations. First, due to the small sample and the retrospective nature of this study, more prospective studies with larger sample size should be performed to confirm the results of this study. Second, the definition of the CSF has no consistent standard. This study adopted the TFC method, while several studies defined that coronary blood flow ≤ TIMI grade II [13], which may lead to conflicting results. Third, we ignore the effect of contrast agent on TFCs during the cardiac cycle. Finally, this study is lack of clinical outcome data, thus the long-term prognosis and treatment effect of nicorandil should be further investigated in patients with the CSF.

## Conclusions

The present study demonstrated that both intracoronary nicorandil and nitroglycerin could improve TFCs in patients with CSF, while the acute effect of nicorandil is superior to nitroglycerin in improving CSF.

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## Disclosure of conflict of interest

None.

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