

Nicorandil improves myocardial function by regulating plasma nitric oxide and endothelin-1 in coronary slow flow

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Background Coronary slow flow (CSF) is a special coronary microvascular disorder. The pathogenesis and effective therapeutics of CSF remain unclear. This study aimed to evaluate the global and regional functions of the left ventricle (LV) and investigate the efficacy of nicorandil in patients with CSF.

Patients and methods Thirty-six patients with CSF in the left anterior descending (LAD) branch and 20 patients with normal coronary arteries were included. Global and regional functions of the LV supplied by LAD were measured using conventional Doppler echocardiography and two-dimensional speckle tracking echocardiography, respectively, within 24 h after coronary angiography. Concentrations of plasma nitric oxide (NO) and endothelin-1 (ET-1) were detected using colorimetry and radioimmunoassay, respectively. The function of the LV and the levels of NO and ET-1 were also investigated before and 90 days after treatment with 15 mg/day of nicorandil.

Results Compared with the control group, the early diastolic peak velocity (E), E/A ratio, and plasma NO levels were lower, whereas the late diastolic peak flow velocity (A) and plasma ET-1 levels were significantly higher in the CSF group ($P < 0.05$). The longitudinal strain rate peak of the LV was reduced significantly in CSF patients ($P < 0.001$). After

treatment, 75% (27/36) of CSF patients were free of chest pain. The values of E peak, E/A ratio, longitudinal strain rate peak, and plasma NO level were increased ($P < 0.001$), whereas the ET-1 level was decreased in CSF patients ($P < 0.001$).

Conclusion Nicorandil may improve chest pain symptoms and the impaired function of the LV, possibly by increasing plasma NO and reducing ET-1 in CSF. *Coron Artery Dis* 26:114–120 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: coronary slow flow, echocardiography, endothelin-1, nicorandil, nitric oxide, speckle tracking

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Background

Coronary slow flow (CSF) is a special phenomenon of coronary microvascular disorder, characterized by delayed opacification of coronary arteries on angiography without obvious lesions in the coronary artery on coronary arteriography (CAG) analysis [1,2]. It has been reported that the incidence of CSF is 7% among patients who undergo coronary angiography suspicious of various cardiovascular diseases [3].

At present, many studies suggest that the diastolic function of CSF patients is impaired but that systolic function shows no significant change [4–6]. However, there are also studies indicating, using conventional echocardiography, that the left ventricle (LV) systolic function is damaged [7,8]. To our knowledge, whether the systolic function of the LV is impaired in cases of CSF remains

controversial at present [8]. Two-dimensional speckle tracking echocardiography is a novel imaging technique that analyzes the motion of heart tissues [9]. At present, this method is greatly applied in various diseases in cardiology, with the advantage of quantitative assessment of regional myocardial function [10,11].

Regarding the potential molecular mechanism, many studies have shown that endothelial dysfunction, which could be caused by many factors such as inflammation, adiposity, and atherogenesis, may be involved in the pathogenesis of CSF [12–14]. It has been reported that increased levels of plasma endothelin-1 (ET-1) and decreased levels of nitric oxide (NO) may be involved in the pathogenesis of CSF [15,16]. Besides, recent studies have also demonstrated that CSF is associated with coronary microcirculation dysfunction [12,17,18].

Nicorandil (*N*-[2-hydroxyethyl] nicotinamide nitrate) is a useful vasodilatory drug for different ischemic cardiac diseases [19]. A recent study has shown that nicorandil

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could prevent endothelial dysfunction through an anti-oxidative mechanism, resulting in increased plasma NO and decreased plasma ET-1, in a diabetic animal model [20]. Furthermore, Tsubokawa *et al.* [21] showed that nicorandil had a preventive effect on the CSF during rotational atherectomy. The same finding was obtained by Juneja *et al.* [22], who demonstrated that the CSF phenomenon in primary percutaneous coronary intervention could be prevented by nicorandil. Although current studies have demonstrated that nicorandil may reduce the incidence of CSF, the potential mechanism of nicorandil on CSF, as well as the improvement of myocardial function by nicorandil, remains rarely investigated.

We hypothesized that nicorandil may prevent endothelial dysfunction and improve the myocardial function of the LV in CSF patients, possibly by regulating the levels of circulating NO and ET-1 in cases of CSF. To prove this assumption, we assessed the global myocardial function of the LV using conventional Doppler echocardiography and the segmental functions supplied by the left anterior descending (LAD) in CSF patients using two-dimensional speckle tracking echocardiography. In addition, the plasma levels of NO and ET-1 were investigated before and after treatment in CSF patients.

Patients and methods

Ethics

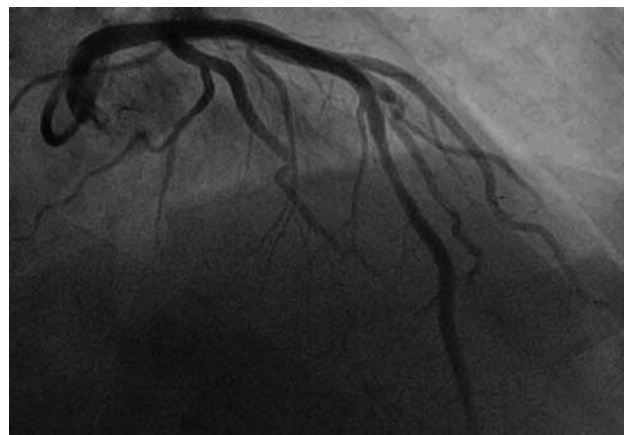
All studies have been approved by the Affiliated Hospital of Qingdao University Ethics Committee and were performed in accordance with ethical standards.

Patients

In the Affiliated Hospital of Qingdao University, a total of 3478 patients underwent CAG from April 2013 to September 2013 because of clinical chest pain suspicious of coronary artery disease. CSF was defined according to the thrombolysis in myocardial infarction (TIMI) flow grade method, and the blood flow of the LAD with or below TIMI grade 2 (i.e. requiring ≥ 3 cardiac cycles to opacify the distal blood vessels) was defined as CSF [23]. Patients with angiographically proven CSF in the LAD were recruited into our study (Fig. 1). Patients with artery stenosis ($>40\%$), congenital heart disease, valvular heart disease, cardiomyopathy, cardiac disease, peripheral vascular disease, hematological system disease, tumor, recent surgical operation, dysfunction of liver, lung, and kidney, and acute and chronic infections were excluded from the study. None of the enrolled patients had prior myocardial infarction. Following CAG, blood testing of high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations was carried out. The clinical data of the selected patients were collected from our hospital database.

Patients with CSF in the LAD were given 5 mg nicorandil (Batch number: B01008970; Chugai Pharmaceutical Co. Ltd, Tokyo, Japan) orally three times a day. The

Fig. 1



A typical coronary angiography image of coronary slow flow in the left anterior descending.

clinical symptoms of the patients were observed 90 days after treatment. Patients were not allowed to take any other drugs that may affect NO and ET-1 levels, such as nitrates, β -blockers, and angiotensin-converting enzyme inhibitors, within 5–7 days before the study and 90 days after using nicorandil.

For investigations involving humans, approval was obtained from the institutional review board of the hospital committee and the study was performed according to the Declaration of Helsinki. Informed consent was provided by each patient.

Coronary arteriography protocols

CAG was performed with a digital subtraction angiography system (Allura Xper FD20; Philips Medical Systems, Best, the Netherlands) using the standard Judkins technique, obtaining images at the rate of 30 frames/s. During CAG, the iopromide (Ultravist 370; Schering AG, Berlin, Germany) contrast and the 6-F diagnostic catheter were used in all patients. The injection speed was 4–5 ml/s for the left coronary artery and 3–4 ml/s for the right coronary artery (RCA). The injection amount was 8–10 ml for the left coronary artery and 6–8 ml for the RCA. We visualized the LAD in a right anterior oblique projection with head angulation of 20–25°, the left circumflex coronary artery (LCX) in a right anterior projection with foot angulation of 20–25°, and the RCA in a normotopia position with head angulation of 30°. All patients were carefully observed in terms of pulse and blood pressure during CAG.

Myocardial function detection

The global functions of the selected patients were assessed with conventional Doppler echocardiography: two-dimensional gray-scale images of the apical two-chamber, apical left ventricular long-axis view, the left

ventricular short-axis basal level, and the apical basal level were collected using conventional Doppler echocardiography within 24 h after CAG and 90 days after treatment [10]. The left ventricular internal diameter at end-diastole (LVIDd), left ventricular internal end-systolic diameter (LVIDs), left ventricular ejection fraction (LVEF), mitral valve flow spectrum of early diastolic peak velocity (E), and late diastolic peak flow velocity (A) were measured using conventional Doppler echocardiography 24 h after CAG, and E/A ratios were calculated. All of the above data were measured to assess the global function of the LV.

The regional functions of the selected patients were evaluated by means of two-dimensional speckle tracking echocardiography: the peak value of the longitudinal strain rate (LSR) of LV segmental systoles supplied by the LAD was measured with GE Echo PAC software using two-dimensional speckle tracking echocardiography for regional functions of the LV. The segments supplied by the LAD included six parts: the basal anterior wall, the mid-anterior, the apical anterior, the basal anteroseptal, the mid-anteroseptal, and the apical septal [24].

Detection of plasma nitric oxide and endothelin-1

Venous blood of a volume of 4 ml was drawn to measure the plasma levels of NO and ET-1 of all the patients 24 h after CAG and 90 days after treatment with nicorandil in the CSF group. The method of colorimetry was used to detect plasma NO concentration, and plasma ET-1 level was examined by means of radioimmunoassay [25].

Statistical analysis

Data were analyzed with SPSS 13.0 statistical software (IBM-SPSS Inc., Armonk, New York, USA). The χ^2 -test was used to enumerate data between groups. Data were expressed as mean \pm SD. The *t*-test was used to compare two independent samples of cardiac function and plasma parameters between the CSF and control groups. If differences in cardiac functions and plasma parameters in the groups before and after nicorandil treatment conformed to Gaussian distribution, the paired *t*-test was used in the analysis. Otherwise, the paired rank-sum test was used. *P* values less than 0.05 indicated that the difference was significant.

Results

Basic characteristics of the enrolled patients

Of the total 3478 patients, 2178 showed coronary artery stenosis above 40%, 1072 cases showed normal coronary blood flow, and 228 showed CSF. The CSF phenomenon was observed in 6.56% (228/3478) of patients. Among the 228 CSF patients, there were 43 for single RCA, 64 for single LAD, 23 for single LCX, 41 for LAD combined with RCA, 28 for LAD combined with LCX, 17 for RCA combined with LCX, and 12 for all three branches. Of the 64 CSF patients with LAD, we selected

Table 1 Baseline clinical characteristics of the participants in the coronary slow flow group and the control group

	Control group (n=20)	CSF group (n=36)	<i>t</i> or χ^2	<i>P</i>
Age (years)	55.7 \pm 4.8	56.8 \pm 5.9	0.761	0.450
Male/female	12/8	21/15	0.015	0.903
Hypertension (%)	35	36.1	0.007	0.934
Diabetes (%)	30	25	0.164	0.686
Smoking (%)	55	52.8	0.026	0.873
HDL-c (mg/dl)	39.85 \pm 7.75	38.97 \pm 7.78	0.410	0.684
LDL-c (mg/dl)	108.10 \pm 30.98	110.42 \pm 25.22	0.303	0.763

CSF, coronary slow flow; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

36 patients for participation in our study (defined as the CSF group), after excluding eight patients for hypertrophic cardiomyopathy, five for aortic valve insufficiency, four for aortic valve stenosis, six for rheumatic heart disease, three for atrial septal defect, and two for ventricular septal defect. Meanwhile, we selected 20 patients with a normal coronary artery (defined as the control group), which showed no significant difference in terms of age, sex, diabetes, hypertension, smoking, and blood lipids compared with the selected CSF group ($P > 0.05$) (Table 1).

Comparison of echocardiography values and levels of circulating nitric oxide and endothelin-1 between the coronary slow flow group and the control group

To assess the integral functions of the LV, the values of LVIDd, LVIDs, LVEF, E peak, A peak, and E/A ratio were measured within 24 h after CAG using conventional Doppler echocardiography. It was found that there were no statistical differences in LVIDd, LVIDs, and LVEF between the CSF group and the control group ($t = 0.318$ – 0.545 , $P > 0.05$). E peak value and E/A ratio were significantly lower ($t = 4.817$ – 9.443 , $P < 0.001$), whereas the A peak value was significantly higher ($t = 3.534$, $P < 0.01$), in the CSF group compared with the control group (Table 2).

Using the two-dimensional speckle tracking technique, we evaluated the regional functions of the LV within 24 h after CAG. Our results showed that LSR peak values of four myocardial segments supplied by the LAD, including the mid-anterior, the mid-anteroseptal, the apical anterior, and the apical septal, were significantly lower than those of the control group ($t = 8.044$ – 12.497 , $P < 0.001$). There was no difference in LSR peak values of the two segments, including the basal anterior and the basal anteroseptal, between the CSF group and the control group ($t = 0.076$ – 0.234 , $P > 0.05$) (Table 2 and Fig. 2a and b).

For further investigating the mechanism of CSF, the levels of circulating NO and ET-1 were also examined within 24 h after CAG. Our present study showed that the plasma NO level was downregulated significantly ($t = 13.134$, $P < 0.001$), whereas the level of ET-1 was

Table 2 Comparison of echocardiographic parameters, longitudinal strain peak values, and plasma markers between the coronary slow flow and control groups

	Control group (n=20)	CSF group (n=36)	t	P
Echocardiographic parameters				
LVEF (%)	57.20±4.30	56.78±4.22	0.356	0.723
LVIDd (mm)	50.75±3.86	50.14±4.11	0.545	0.588
LVIDs (mm)	27.55±2.35	27.36±2.00	0.318	0.752
E peak value	82.50±11.68	68.14±10.11	4.817	<0.001
A peak value	68.85±9.50	78.28±9.60	3.534	<0.01
E/A	1.20±0.10	0.88±0.13	9.443	<0.001
LS peak values				
Basal myocardial segment				
Before interval	2.34±0.21	2.33±0.18	0.234	0.816
Antetheca	2.34±0.23	2.35±0.16	0.076	0.94
Middle myocardial segment				
Before interval	1.88±0.13	1.30±0.20	11.97	<0.001
Antetheca	1.76±0.12	1.51±0.11	8.044	<0.001
Apical myocardial segment				
Before interval	2.20±0.12	1.74±0.18	10.122	<0.001
Antetheca	1.66±0.17	1.00±0.20	12.497	<0.001
Plasma markers				
NO (μmol/l)	39.63±3.82	23.96±4.51	13.134	<0.001
ET-1 (pg/ml)	4.91±1.36	12.49±1.43	19.401	<0.001

A, late diastolic peak flow velocity; CSF, coronary slow flow; E, mitral valve flow spectrum of early diastolic peak velocity; ET-1, endothelin-1; LVEF, left ventricular ejection fraction; LVIDd, left ventricular internal diameter at end-diastole; LVIDs, left ventricular internal end systolic diameter; NO, nitric oxide.

upregulated significantly ($t=19.401$, $P<0.001$), in the CSF group compared with the control group (Table 2).

Comparison of echocardiography values and levels of circulating nitric oxide and endothelin-1 before and after treatment in patients with coronary slow flow

According to the criterion of subjective descriptions of patients with respect to improvement in chest pain symptoms, chest pain symptoms of 27 patients in the CSF group after nicorandil treatment improved and the remission rate was 75%.

Using conventional Doppler echocardiography, we found that the E peak value ($t=28.847$, $P<0.001$) and E/A ratio ($Z=3.757$, $P<0.001$) had increased significantly in the CSF group after treatment with nicorandil. There was no significant improvement in the A peak value after treatment ($Z=0.869$, $P>0.05$) (Table 3).

After treatment with nicorandil, the LSR peak values of three myocardial segments including the mid-anteroseptal, the apical anterior, and the apical septal increased ($t=8.757-23.96$, $P<0.001$). There was no difference in LSR peak value of the mid-anterior before and after treatment ($t=0.899$, $P>0.05$) (Table 3 and Fig. 2b and c).

In addition, our results found that the concentration of circulating NO increased ($t=16.375$, $P<0.001$), whereas the ET-1 level decreased significantly, after treatment with nicorandil in the CSF group ($t=26.162$, $P<0.001$) (Table 4).

Comparison of post-treatment echocardiography values and levels of circulating nitric oxide and endothelin-1 with those in the control group

For assessing the extent of improvement in CSF patients as a result of treatment with nicorandil, we compared the post-treatment echocardiography values and levels of plasma NO and ET-1 with those in the control group. It was found that the E peak value had become normal in the CSF group after treatment ($t=1.990$, $P>0.05$), whereas the E/A ratio A peak value was still higher than that in the control group ($t=3.717-7.061$, $P<0.001$) (Table 4). The E/A ratio was lower than that in the control group ($t=7.061$, $P<0.001$) (Table 4).

In terms of regional function assessment of the LV, the results showed that the LSR peak values of four segments, including the mid-anterior, the apical anterior, and the apical septal, in the CSF group after treatment were still lower than those of the control group ($t=4.195-8.169$, $P<0.001$) (Table 4).

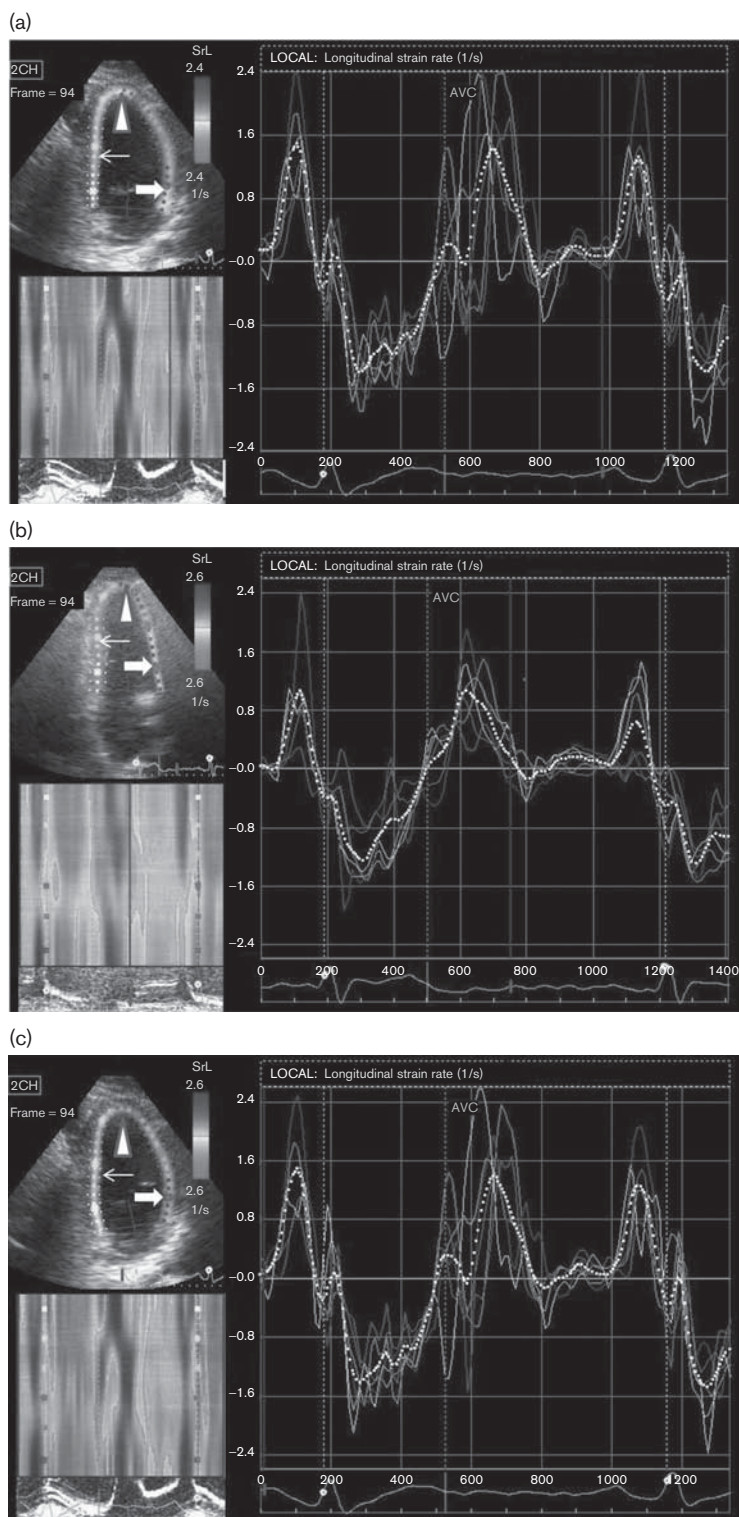
In addition, the plasma concentrations of NO in the CSF group with nicorandil treatment increased greatly but did not reach normal levels as in the control group ($t=8.121-9.978$, $P<0.001$) (Table 4).

Discussion

In the present study, myocardial global function was assessed by conventional echocardiography, and segmental functions of the LV supplied by the LAD were evaluated by means of two-dimensional speckle tracking echocardiography in the present study. The results of the conventional echocardiography showed that the E peak value and E/A ratio in the CSF group were lower than that in the control group (Table 2), suggesting that the diastolic function was impaired in CSF patients. Meanwhile, we also found that there was no significant difference in LVEF between the two groups (Table 2), suggesting that the overall systolic function of the LV was not damaged in the CSF group compared with the normal values. This may be explained by the fact that LV diastolic function is more susceptible to ischemia than is systolic function [26]. Gunes *et al.* [8] reported that patients with CSF had impaired diastolic and regional LV systolic functions on the basis of myocardial tissue Doppler velocities. In accordance with the above finding, our results from two-dimensional speckle tracking echocardiography showed that the LSR peak values of four myocardial segments supplied by the LAD were significantly lower compared with that of the control group (Table 2 and Fig. 2a and b). These results suggested that CSF patients had segmental systolic dysfunctions of the LV, although LV global systolic function was normal.

Vascular endothelial dysfunction has been demonstrated to be involved in the pathogenesis of CSF [12]. Valeriani *et al.* [27] reported that endothelial NO synthase activity, as well as NO concentration, was decreased in patients

Fig. 2



Longitudinal strain rate (LSR) peak images of patients in the control group (a) and coronary slow flow group before (b) and after (c) treatment. (a) An apical two-chamber heart tangent plane is shown in the top left corner of the picture, on which the basal anterior segment (thick arrow), the mid-anterior segment (thin arrow), the apical anterior segment (triangle), and the LSR curve independent of the present study are shown. The white dotted line represents the overall strain rate curve. (b) Compared with the control group, the LSR peak value of the anterior basal segment (thick arrow) did not change significantly, whereas the LSR peak values of the mid-anterior segment (thin arrow) and the apical anterior segment (triangle) decreased. The overall strain rate (dashed white line) was significantly decreased. (c) Compared with pretreatment values, there were changes in the basal anterior segment (thick arrow) and mid-anterior segment (thin arrow). The peak value of LSR had no change, and the LSR peak values of the apical anterior segment (triangle) and the whole LSR peak value (white dotted line) were significantly increased.

Table 3 Comparisons of echocardiographic parameters, longitudinal strain peak values and plasma markers in the coronary slow flow group before and after treatment

	E peak value	A peak value	E/A	NO ($\mu\text{mol/l}$)	ET-1 (pg/ml)	Middle segment		Apical segment	
						Before interval	Antetheca	Before interval	Antetheca
Before treatment ($n=36$)	68.14 \pm 10.11	78.28 \pm 9.60	0.88 \pm 0.13	23.96 \pm 4.51	12.49 \pm 1.43	1.30 \pm 0.20	1.51 \pm 0.11	1.74 \pm 0.18	1.00 \pm 0.20
After treatment ($n=36$)	76.53 \pm 10.23	78.58 \pm 9.33	0.97 \pm 0.13	29.52 \pm 3.53	7.19 \pm 0.75	1.62 \pm 0.21	1.52 \pm 0.15	1.97 \pm 0.23	1.24 \pm 0.18
<i>t</i> or <i>Z</i>	28.847 ^a	0.8692	3.7572	16.3751	26.1621	9.944	0.899	8.757	23.96
<i>P</i>	<0.001 ^a	0.385 ^b	<0.001 ^b	<0.001 ^a	<0.001 ^a	<0.001 ^a	0.385 ^a	<0.001 ^a	<0.001 ^a

A, late diastolic peak flow velocity; E, mitral valve flow spectrum of early diastolic peak velocity; ET-1, endothelin-1; NO, nitric oxide.

^aPaired test *t* value.

^bIndicates rank-sum test *Z* value.

Table 4 Comparisons of echocardiographic parameters, longitudinal strain peak values, and plasma markers between the coronary slow flow group after treatment and the control group

	E peak value	A peak value	E/A	NO ($\mu\text{mol/l}$)	ET-1 (pg/ml)	Middle segment		Apical segment	
						Before interval	Antetheca	Before interval	Antetheca
Control group ($n=20$)	82.50 \pm 11.68	68.85 \pm 9.50	1.20 \pm 0.10	39.63 \pm 3.82	4.91 \pm 1.36	1.88 \pm 0.13	1.74 \pm 0.13	2.21 \pm 0.12	1.66 \pm 0.17
CSF group after treatment ($n=36$)	76.53 \pm 10.23	78.58 \pm 9.33	0.97 \pm 0.13	29.52 \pm 3.53	7.19 \pm 0.75	1.62 \pm 0.21	1.52 \pm 0.15	1.97 \pm 0.23	1.24 \pm 0.18
<i>t</i>	1.99	3.717	7.061	9.978	8.121	5.206	5.56	4.195	8.169
<i>P</i>	>0.05	<0.001	<0.001	<0.001	<0.001	<0.001	0.385	<0.001	<0.001

A, late diastolic peak flow velocity; CSF, coronary slow flow; E, mitral valve flow spectrum of early diastolic peak velocity; ET-1, endothelin-1; NO, nitric oxide.

with microcirculation disorder. Another study by Celebi *et al.* [28] showed that ET-1 concentration was increased in CSF patients. In accordance with the above findings, our results also showed that the plasma NO concentration was decreased and the concentration of ET-1 was increased in the CSF group compared with the control group (Table 2), suggesting that the combination of decreased level of plasma NO and increased level of ET-1 may be involved in the formation and development of CSF. Chen *et al.* [29] reported that nicorandil had vasodilatory effects on the coronary artery with a diameter of 100–200 μm . Besides its direct vasodilatory effect, the fact that nicorandil could improve vascular endothelial dysfunction has been demonstrated [30]. Another report by Serizawa *et al.* [20] has reported that nicorandil could prevent endothelial dysfunction by regulating NO and ET-1. In our study, nicorandil was applied in 36 CSF patients with LAD, and the results showed that 27 patients with chest pain symptoms had recovered. Functional analysis showed that diastolic function had improved after treatment (Table 3). LSR peak values of three myocardial segments increased after treatment (Table 3 and Fig. 2b and c). Besides, we also found that the concentration of plasma NO had increased in patients with CSF after treatment with nicorandil, whereas the plasma ET-1 concentration had decreased (Table 4). These results suggest that nicorandil could improve chest pain symptoms and the cardiac functions of the LV, possibly by regulating the plasma levels of NO and ET-1 in CSF.

Besides, our study further compared the post-treatment echocardiographic values and levels of circulating NO and ET-1 with those in the control group to assess the

extent of improvement in CSF patients by treatment with nicorandil (Table 4). Our results suggested that nicorandil could not improve the hemodynamic disorder and LV function to the normal state, although it could improve the symptoms of CSF and the impaired myocardial function of the LV greatly, as well as increasing plasma NO and decreasing plasma ET-1. Our finding suggested that nicorandil combined with other effective drugs is of considerable value in the treatment of CSF [31]. Further studies are needed to cure CSF completely.

We must point out that the TIMI method is an important index for evaluating the effect of coronary blood flow [32]. It is more direct and accurate to assess the treatment effects of nicorandil by using the TIMI method than by echocardiographic evaluation of LV myocardial function. However, because most CSF patients refused to accept the second CAG, echocardiographic myocardial function was used as the evaluation index in this study. In addition, our study was limited by a small number of cases. A randomized optimal group and parallel controls were not used in the treatment of CSF with nicorandil. Thus, a large population of CSF patients and more accurate methods of assessing CSF should be further studied.

Conclusion

CSF patients presented with both diastolic and regional systolic dysfunctions of the LV. The combination of decreased level of circulating NO and increased level of plasma ET-1 may be involved in the pathophysiological mechanism of CSF. Nicorandil shows beneficial efficacy in CSF by improving chest pain symptoms and cardiac function, possibly by upregulating the level of plasma NO and downregulating the level of ET-1.

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Conflicts of interest

There are no conflicts of interest.

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