Acute Effects of Intracoronary Nitroglycerin and Diltiazem in Coronary Slow Flow Phenomenon

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Background: The coronary slow flow phenomenon (CSFP) is a coronary microvascular disorder angiographically defined by delayed opacification of the distal vasculature in the absence of obstructive coronary artery disease. We aimed to investigate and compare the effects of intracoronary nitrate and diltiazem on thrombolysis in myocardial infarction frame count (TFC) in patients with CSFP during coronary angiography.

Methods: Sixty patients with CSFP were randomly divided into 2 groups. The first group is nitroglycerin group with 30 patients (22 men; mean [SD] age, 50 [12] years), and the second is diltiazem group with 30 patients (27 men; mean age, 54 ± 11 years); intracoronary 5-mg diltiazem or 250-μg nitroglycerin was administered. Heart rate, systolic and diastolic blood pressures, and TFCs in all 3 coronaries were recorded before and after administering these medications.

Results: After nitroglycerin administration, systolic and diastolic blood pressures decreased, heart rates significantly increased, and TFCs decreased in all coronaries ($P < 0.001$ for 3 coronaries). After the application of intracoronary 5-mg diltiazem, heart rate, systolic and diastolic blood pressures, and TFCs were found significantly lower than predrug values ($P < 0.001$ for all values). When the percent TFC reductions, after the application of intracoronary diltiazem or nitroglycerin, in left anterior descending coronary artery, circumflex coronary artery, and right coronary artery were evaluated, diltiazem significantly reduced the TFCs of the left anterior descending coronary artery and circumflex coronary artery compared with nitroglycerin ($P < 0.01$ for both coronaries).

Conclusion: Both intracoronary diltiazem and nitroglycerin improve the TFCs in CSFP, and intracoronary diltiazem is superior to nitroglycerin in reducing TFCs in CSFP.

Key Words: coronary slow flow phenomenon, intracoronary nitroglycerin, intracoronary diltiazem

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Coronary slow flow phenomenon (CSFP) is angiographically defined by delayed distal vasculature opacification in patients with angiographically normal or near-normal coronary arteries.[1,2] The frequency of CSFP is approximately 1% to 7 % in patients undergoing routine coronary angiography and is often associated with chest pain.[3–5] It is clinically distinct from other coronary microvascular disorders observed in conditions such as distal embolism after coronary reperfusion therapy, coronary artery spasm, coronary artery ectasia, myocardial dysfunction, valvular heart disease, air embolism, or connective tissue disorders.[2]

This angiographic phenomenon showing slow delayed opacification of vessels was first described in 6 patients with typical angina pectoris by Tambe et al.[1] in 1972. Coronary slow flow phenomenon is most commonly seen in male smokers. Almost 80% of the patients experience recurrent chest pain, with nearly 20% of them requiring hospital readmission for an acute exacerbation. Electrocardiographic and/or scintigraphic evidence of ischemia was observed in fewer than half the patients.[3]

The mechanisms responsible for the CSFP remain obscure. Potential causes include endothelial dysfunction, microvascular dysfunction, small vessel disease, diffuse atherosclerosis, vasomotor dysfunction, and inflammation.[6–9] Increased resting arterial resistance is the most plausible hypotheses in the pathogenesis of CSFP.

There is no definite treatment in patients with CSFP. As the findings in CSFP are consistent with the hypothesis that the CSFP represents a distinct microspastic form of angina pectoris, nitrates and calcium channel blockers may be beneficial for patients with CSFP owing to their antianginal and antispastic properties. In this study, we aimed to investigate and compare the effects of intracoronary nitroglycerin and diltiazem on thrombolysis in myocardial infarction (TIMI) frame counts (TFC) in patients with CSFP during coronary angiography.

MATERIALS AND METHODS

Study Population

This prospective and open-label randomized trial was performed between February 2008 and January 2010. Sixty patients with angiographically normal or near-normal (<40% stenosis) coronary arteries, and CSFP in one of the coronary arteries were included in the study.

Coronary slow flow phenomenon was defined as a corrected TFC exceeding standard reference values +2 times the standard deviation in 1 or more vessels. The mean (SD) reference cutoff values for normal TIMI frame counts were the following: 36.2 (2.6) frames for the left anterior descending (LAD) coronary artery, 22.2 (4.1) frames for the circumflex (CX) coronary artery, and 20.4 (3.0) frames for the right coronary artery (RCA). The mean (SD) corrected cutoff value for the LAD coronary artery was 21.1 (1.5) frames as previously described.[10]

Patients with known allergy to diltiazem or nitroglycerin, on treatment with calcium channel blockers or nitrates, acute coronary syndrome, history of coronary artery disease, coronary vasospasm, coronary artery ectasia, valvular heart disease, cardiomyopathy, left ventricular systolic dysfunction (ejection fraction, <50%), bradycardia, atrioventricular conduction disease, hypotension during coronary angiography, renal and hepatic insufficiency, connective tissue disorder, autoimmune disease,

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malignancy, and infection were excluded. Patients were also excluded when the TIMI-2 flow occurred in the context of a provocative ischemic maneuver, such as coronary angioplasty. This study was approved by the local ethical committee of Erciyes University, and all patients gave written informed consent.

The patients were randomly divided into 2 groups; the first group is nitroglycerin group with 30 patients (22 men; mean [SD] age, 50 [12] years) and the second group is diltiazem group with 30 patients (27 men; mean [SD] age, 54 [11] years); and intracoronary diltiazem or nitroglycerin was performed to the patients during coronary angiography. Heart rate, TFC, and systolic and diastolic blood pressure of patients were recorded before and after administering these medications.

Coronary Angiography and TIMI Frame Count

Coronary angiography was performed by a femoral approach using standard Judkins technique with Philips INTEGRIS H 5000 or Toshiba Infinix CC-i monoplane cardiac angiography system at 25 frames per second. During coronary angiography, iopromide (Ultravist-370) or iohexol (Omnipaque, 350 mg/mL) was used as the contrast agent and an injection of 6 to 8 mL contrast medium was given manually at each position.

Coronary arteries were visualized in the left and right oblique planes with cranial and caudal angles. Left ventriculography was done in a right and left anterior oblique view using a pigtail catheter. Additional angiographic images were taken after diltiazem or nitroglycerin administration.

Angiographic data were subsequently analyzed by an experienced investigator. Coronary flow rates of all subjects were determined by the TIMI frame count (CTFC) method first described by Gibson et al.[10] The number of cineframes required for contrast to first reach standardized distal coronary landmarks was measured. The first frame was defined as the one in which concentrated dye extended across the entire width of the origin of the artery, touching both borders of the lumen. The distal coronary landmarks used for analysis were the distal bifurcation at the apex of the LAD coronary artery, the distal bifurcation of the major obtuse marginal, or the main CX coronary artery, whichever was larger, and the site of origin of first branch at the crux or its posterolateral extension for the RCA. The final frame counted was that in which contrast first reaches the distal landmark branch without necessity of full opacification. The LAD coronary artery is usually longer than the CX coronary artery and RCA, the TFC for the LAD coronary artery is often higher. Therefore, the LAD coronary artery frame counts were corrected by dividing by 1.7 to obtain the corrected TFC as described earlier. Percent reduction in TIMI frame count was measured as [(TFC before intracoronary drug administration − TFC after intracoronary drug administration) / TFC before intracoronary drug administration] × 100.TIMI frame count in the LAD coronary artery and left CX coronary artery were assessed in a right anterior oblique projection with caudal angulation and RCA in left anterior oblique projection with cranial angulation.

Laboratory Measurements

Blood samples were drawn from an antecubital vein from all patients before coronary angiography after a 12-hour overnight fasting for the measurement of fasting plasma glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride levels. Blood samples were collected in EDTA-treated tubes and immediately centrifuged and plasma was obtained. Fasting blood glucose, total cholesterol, HDL cholesterol and triglyceride levels were measured enzymatically by the auto analyzer. Measurement of LDL cholesterol level was performed by Friedewald formula using the equation [LDL = total cholesterol − (HDL+ (triglycerides/5))]. The levels of urea nitrogen and creatinine were also determined using a Beckman Coulter Synchron LX20 Clinical System. Hematologic parameters were measured on an automatic blood counter.

Intracoronary Diltiazem and Nitroglycerin Administration

Five-milligram diltiazem (Diltizem; Mustafa Nevzat Pharmaceuticals, Inc., İstanbul, Turkey) was diluted with 2.5 mL of saline and 250 μg glyceryl trinitrate (Perlinganit Adeka Pharmaceuticals Inc., Samsun, Turkey) was diluted with 2.5 cc of saline before intracoronary administration. Blood pressure and heart

TABLE 1. Comparison of Clinical Characteristics of Both Groups

Parameters	Nitroglycerin n = 30	Diltiazem n = 30	*P*
Age, mean (SD), yrs	50 (12)	54 (11)	>0.05
Sex, M/F	22/8	27/3	>0.05
Diabetes mellitus, n (%)	4 (13)	3 (10)	>0.05
Hypertension, n (%)	12 (40)	20 (66)	<0.05
Smoker, n (%)	9 (30)	13 (43)	>0.05
BMI, mean (SD), kg/m^2	26.2 (3.1)	28.4 (3.4)	<0.05
β-Blockers, n (%)	6 (20)	7 (23)	>0.05
Statin, n (%)	7 (23)	7 (23)	>0.05
ARB, n (%)	9 (30)	15 (50)	>0.05
ACE inhibitors, n (%)	1 (3)	2 (6)	>0.05
Cholesterol, mean (SD)	174.60 (36.21)	187.53 (31.87)	>0.05
HDL, mean (SD)	37.65 (10.50)	36.10 (6.94)	>0.05
LDL, mean (SD)	109.38 (29.41)	112.90 (29.71)	>0.05
Triglyceride, mean (SD)	135.20 (67.47)	196.13 (90.16)	<0.05
Glucose, mean (SD)	113.23 (44.69)	110.90 (51.97)	>0.05
EF, mean (SD), %	64.5 (7.8)	67.3 (8.1)	>0.05

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; EF, ejection fraction; F, female; M, male.

TABLE 2. Heart Rate and Systolic and Diastolic Aortic Pressures in Both Groups Before and After Injection of Nitroglycerin and Diltiazem

	Nitroglycerin			Diltiazem		
	Before Injection n = 30 (Mean [SD])	After Injection n = 30 (Mean [SD])	P	Before Injection n = 30 (Mean [SD])	After Injection n = 30 (Mean [SD])	P
Heart rate, beats/min	75.6 (12.1)	87.4 (17.2)	<0.001	83.0 (6.6)	73.7 (13.0)	<0.001
Systolic aortic pressure, mm Hg	115.2 (16.6)	98.0 (17.1)	<0.001	125.5 (19.6)	111.0 (12.8)	<0.001
Diastolic aortic pressure, mm Hg	76.8 (12.1)	65.2 (10.0)	<0.001	81.8 (13.0)	72.7 (9.3)	<0.001

rate were obtained after detecting CSFP during coronary angiography and diltiazem or glyceryl trinitrate was randomly administered. A minute later after administering 5-mg diltiazem or 250-μg glyceryl trinitrate, blood pressure and heart rate were recorded and coronary angiography were performed again to evaluate the effects of these drugs on TFC.

Statistical Analysis

SPSS 13.0 (SPSS Science, Chicago, IL) for Windows was used for statistical analysis.

The Kolmogorov-Smirnov test was used to evaluate whether the distribution of continuous variables was normal. Continuous variables are presented as mean (SD) and categorical variables as percentages. Comparison of categorical and continuous variables between the 2 groups was performed using the χ^2 test and independent sample *t* test, respectively. Pretreatment and posttreatment numeric variables with normal distribution were compared using the paired *t* test. $P < 0.05$ was considered statistically significant.

RESULTS

Among the 60 participants in this angiographic study, baseline angiography demonstrated normal epicardial coronary arteries in all patients. Of the 30 major epicardial coronary vessels systematically assessed in the nitroglycerin group, at baseline, CSFP was detected most commonly in LAD coronary artery (93%), followed by CX coronary artery (70%) and (50%) right coronary arteries. In the diltiazem group, it was similar as most commonly in LAD coronary artery (93%) followed by CX coronary artery (53%) and (36%) right coronary arteries. Intracoronary administrations of both drugs, nitroglycerin and diltiazem, were well tolerated.

Most of the clinical characteristics except history of hypertension, body mass index, and triglyceride levels were similar between the 2 groups as shown in Table 1.

After intracoronary 250-μg nitroglycerin administration, systolic and diastolic blood pressures were decreased ($P < 0.001$), and heart rates were significantly increased ($P < 0.001$; Table 2). Thrombolysis in myocardial infarction frame count after the application of intracoronary nitroglycerin to coronary vessel with slow flow was found significantly lower than TFC values before the application of intracoronary nitroglycerin ($P < 0.001$; Table 3).

After the application of intracoronary 5-mg diltiazem, heart rate and systolic and diastolic blood pressures of the patients were found significantly lower than predrug values ($P < 0.001$; Table 2). Thrombolysis in myocardial infarction frame counts after the application of intracoronary diltiazem were found significantly lower than TIMI frame values before the application of intracoronary diltiazem ($P < 0.001$; Table 3).

The comparison of percent TFC reductions after the application of intracoronary 5-mg diltiazem and 250-μg nitroglycerin to LAD coronary artery, CX coronary artery, and RCA showed that diltiazem significantly reduced TFCs of LAD coronary artery and CX coronary artery compared with nitroglycerin ($P = 0.002$ and $P = 0.002$). However, in RCA, there was a nonsignificant trend in the same direction in TFC percent reduction values ($P = 0.12$) (Fig. 1).

DISCUSSION

Previous studies showed that dipyridamole, mibefradil, nicorandil, and atorvastatin improved coronary blood flow in CSFP.[11–14] In the present study, we investigated and compared the effects of intracoronary nitroglycerin and intracoronary diltiazem therapy on TFCs in patients with CSFP. Both intracoronary diltiazem and nitroglycerin improved the TFCs in patients with slow coronary flow, and further analysis demonstrated that intracoronary diltiazem improved TFCs more than intracoronary nitroglycerin, especially in LAD and CX coronary arteries. These findings are consistent, as the increased resting arterial resistance is the most plausible hypotheses in the pathogenesis of CSFP. Furthermore, intracoronary diltiazem may be more useful, as it may act not only on coronaries but also on myocardial contraction.

Primary effect of nitroglycerin on the coronary artery system is dilating the epicardial coronary arteries. However, coronary and peripheral arterioles with a diameter of less than

TABLE 3. Thrombolysis in Myocardial Infarction Frame Count Values Before and After Injection of Diltiazem and Nitroglycerin

	Nitroglycerin			Diltiazem		
	Before Injection n = 30 (Mean [SD])	After Injection n = 30 (Mean [SD])	P	Before Injection n = 30 (Mean [SD])	After Injection n = 30 (Mean [SD])	P
cLAD	36.82 (9.05)	26.09 (11.21)	<0.001	32.10 (9.80)	17.20 (9.03)	<0.001
LAD coronary artery	62.61 (15.22)	41.75 (13.68)	<0.001	54.67 (16.29)	29.30 (5.48)	<0.001
CX coronary artery	37.54 (11.62)	28.12 (11.01)	<0.001	37.77 (14.33)	22.82 (9.86)	<0.001
RCA	43.93 (22.82)	35.43 (20.45)	<0.001	40.36 (11.41)	26.91 (9.51)	<0.001

cLAD indicates corrected TIMI frame count for LAD coronary artery.

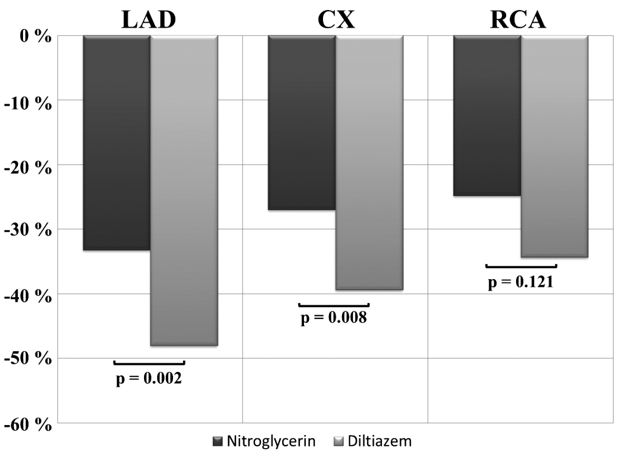

FIGURE 1. Thrombolysis in myocardial infarction frame count percent reductions after intracoronary nitroglycerin and diltiazem injections.

100 μm are relatively more resistant to nitroglycerin,[15] but some of the studies showed that nitrates may act on resistance vessels in acute phase of administration in higher doses.[16,17]

In normal subjects, Abaci et al.[18] showed that nitrate increased TFC. This was explained by the dilatation of coronary arteries. As the diameters of the coronary arteries increase by dilatation, a wide artery will have larger blood volume than a narrow artery, and more time (ie, a higher TFC) may be required for a constant volume of contrast agent to reach the distal anatomic landmark in normal healthy subjects. In patients with CSFP, conflicting results were obtained about the effects of nitrates on coronary flow.[5,13,19] Some of them have shown no change, whereas others decreased or increased coronary flow after administration of nitrates.

Sezgin et al.[20] demonstrated that plasma nitric oxide levels were reduced in patients with CSFP and inversely correlated with TFC. Nitrates may improve CSFP, as after entering the vascular smooth muscle, nitrates are converted to nitric oxide or *S*-nitrosothiols, which active intracellular guanylate cyclase that produces cyclic guanosine monophosphate, which causes smooth muscle relaxation. Smooth muscle relaxation causes vasodilatation both in arteries (including coronary) and veins; however, the vasodilator effect of nitrates is prominent in venous circulation. This effect reduces preload, which in turn reduces myocardial wall tension and O_2 requirements. In our study, intracoronary nitroglycerin decreased TFC in patients with CSFP. This improvement may be due to reduced preload and microvascular dilatation, which may be seen early period of nitroglycerin infusion.[16]

In the study performed by Mangieri et al.,[5] intracoronary 0.56-mg/kg dipyridamole or 100 μg of nitroglycerin infusion was given in patients with CSFP. Baseline heart rate and blood pressure were not affected by nitroglycerin infusion; but during dipyridamole infusion, baseline heart rate was significantly increased and mean blood pressure decreased. Nitroglycerin did not affect coronary blood flow; however, dipyridamole infusion significantly improved coronary blood flow.[5] As nitroglycerin has dose-dependent response on coronary arteries, this different result may be due to a low dose, such as 100 μg, intracoronary nitroglycerin administration, which was 250 μg in our study.[16,17] Sadamatsu et al. showed that 1000-μg nitroglycerin improved coronary blood flow in patients with CSFP, which supports the data that higher doses improve CSFP.[21]

Calcium channel blockers inhibit the flow of extracellular calcium through ion-specific channels. When inward calcium flux is inhibited, these agents afford a reduction in vascular smooth muscle tone, resulting in vasodilation and a lowering of blood pressure. In addition, in cardiac muscle, contractility is reduced and the sinus pacemaker and atrioventricular conduction velocities are slowed. Intracoronary injection of diltiazem decreases blood pressure, but the main effect is the significant decrease of coronary arterial resistance, which causes transient vasodilation of the coronary resistance vessels with no change in coronary blood flow.[22]

Our angiographic and therapeutic study demonstrated that calcium channel blocker diltiazem markedly improves angiographic coronary flow rates in patients with the CSFP. The findings are consistent with the hypothesis that coronary microspasm plays an important role in the pathogenesis of the CSFP. Beltrame et al. had also demonstrated that a calcium L-channel blocker mibefradil markedly improved angiographic coronary flow rates in patients with CSFP, and had a major effect in ameliorating anginal symptoms resulting in improved physical well being.[12] However, mibefradil was withdrawn from general therapeutic availability by the manufacturing company primarily because of its inhibition of cytochrome P450 3A4, resulting in potential accumulation of coadministered drugs metabolized via this pathway.

When these 2 therapeutic regimes were compared, intracoronary diltiazem was more effective than nitroglycerin in CSFP. This may be due to prominent antispastic properties and negative inotropic effects of diltiazem. Jones et al.[17] demonstrated that nitroglycerin dilates coronary arterioles and arteries; however, the dilation is transient for arterioles but sustained for arteries in which waning of arteriolar dilation is suggested to be related to autoregulatory escape from dilation by nitroglycerin. Therefore, diltiazem may be a better choice in CSFP as it acts more effectively and has longer action of duration.

Finally, in this angiographic study, we have demonstrated that both intracoronary nitroglycerin and intracoronary diltiazem improved TFCs in CSFP. Furthermore, intracoronary diltiazem was more effective than intracoronary nitroglycerin in CSFP. These results implicate that nitrates and diltiazem may be effective in the treatment of CSFP; however, new studies are needed to investigate the efficacy of oral nitrate and diltiazem.

Study limitations. In this study, we have a limited number of subjects with CSFP. In addition, the patients included in the study are mostly male, which could affect the results. Moreover, injection of dye during systole or diastole was not taken into consideration, which could affect the TFC.

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