Coronary Microvascular Dysfunction in Patients With Microvascular Angina

Analysis by TIMI Frame Count

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Abstract: We have previously reported that angina pectoris persists in patients with coronary microvascular spasm (MVS) even on calcium channel blockers. Because measurement of myocardial lactate production in the coronary sinus is necessary to diagnose MVS, a more feasible diagnostic method needs to be developed. In this study, we examined the diagnostic significance of Thrombolysis in Myocardial Infarction (TIMI) frame count, a marker of coronary blood flow, in 131 consecutive patients who underwent provocation test for coronary spasm with acetylcholine (ACh). Epicardial coronary spasm (ES) was diagnosed as more than 75% of ACh-induced vasoconstriction noted by coronary angiography. MVS was diagnosed as ACh-induced myocardial ischemia (chest pain, ischemic ECG changes, and myocardial lactate production) without ES. TIMI frame count was significantly increased in patients with MVS alone (n = 35) and those with ES + MVS (n = 16) compared with those with ES alone (n = 53) or those with no myocardial ischemia (Normal, n = 27) either before and after intracoronary ACh and even after intracoronary isosorbide dinitrate (ISDN) in both the left anterior descending (LAD) and the left circumflex coronary artery (LCX). TIMI frame count in LAD correlated well to that in LCX in patients with MVS, suggesting diffuse impaired coronary microcirculation in the myocardium. These results suggest that increased TIMI frame count in response to ACh reflects microvascular dysfunction in MVS and that ISDN may not be enough to relieve MVS. Thus, TIMI frame count may be useful to diagnose MVS without requiring coronary sinus catheterization or myocardial lactate production measurement.

Key Words: microvascular spasm, TIMI frame count, ISDN, coronary spasm

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Chest pain with a normal coronary arteriogram remains a dilemma for diagnosis of coronary spasm including epicardial spasm (ES) and/or microvascular spasm (MVS) or noncardiac chest symptoms.[1–3] Calcium channel blockers (CCBs) are effective to diminish chest symptoms for patients with ES; however, MVS persists even on CCBs, resulting in an impaired quality of life.[1] Coronary MVS can cause myocardial ischemia even in the absence of epicardial coronary stenosis or obstruction in humans.[1,4] Furthermore, we have recently demonstrated that coronary MVS contributes to the occurrence of angina in a quarter of patients with ES.[5] At present, MVS can be diagnosed only by provocation test with intracoronary acetylcholine (ACh) or ergonovine, with measurement of lactate production in the coronary sinus, but these invasive methods limit the usefulness of the provocation test. Thus, a more feasible diagnostic method for MVS needs to be developed.

Thrombolysis in Myocardial Infarction (TIMI) frame count is a simple, reproducible, objective, and quantitative index of coronary blood flow.[6] However, no studies have ever examined whether or not TIMI frame count is useful to diagnose MVS. Thus, in the present study, we examined the usefulness of TIMI frame count to diagnose MVS.

METHODS

This study was reviewed and approved by the Ethical Committee of our hospital. An informed consent for provocation test for coronary spasm with acetylcholine (ACh) was given by all patients.

Study Population

We examined 131 consecutive patients (62 men and 69 women) with chest pain and normal coronary arteriograms (CAG) who underwent an ACh provocation test with myocardial lactate production measurement between January 1995 and July 2000. All cardiovascular medications, except sublingual nitroglycerin, were discontinued at least 24 hours before the test, and no patient had received long-acting CCBs before the procedure.

Definition of ES and MVS

Epicardial coronary spasm (ES) was defined when graded doses of intracoronary ACh (10, 30, and 100 μg) induced more than 75% vasoconstriction by coronary angiography.[7] The degree of vasoconstriction was normalized by the diameter obtained after intracoronary administration of isosorbide dinitrate (ISDN) administration, which was measured with calipers in a blind manner.[7] For measurement of myocardial lactate production, paired 2-mL samples of blood were

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collected simultaneously from the ascending aorta and the coronary sinus. MVS was diagnosed when 10 or 30 μg of intracoronary ACh induced myocardial ischemia (2 or more signs out of chest pain, ischemic ECG changes, and myocardial lactate production), as previously reported.[5] The myocardial lactate extraction ratio was calculated as the ratio of the coronary arterial–venous difference in lactate concentration to the arterial concentration. Myocardial lactate production (negative extraction ratio) was considered to be evidence of myocardial ischemia.

Data Collection

Baseline demographic information (including age and sex), coronary risk factors (hypercholesterolemia, smoking, hypertension, diabetes mellitus, and family history of ischemic heart disease) were recorded for each patient. Hypercholesterolemia was defined as total cholesterol ≥220 mg/dL. Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or the use of antihypertensive drug(s). Diabetes was defined as fasting blood sugar ≥140 mg/dL, blood sugar during a 75 g oral glucose tolerance test ≥200 mg/dL, or the use of antidiabetic drug(s).

TIMI Frame Count

TIMI frame count was assessed by a single observer (H.S.), who was blinded to clinical diagnosis of MVS or ES. All coronary angiograms were filmed in a speed of 30 frames per second.[6] TIMI frame count was measured to first reach a standardized distal landmark in the left anterior descending (LAD) and the left circumflex coronary artery (LCX), using a frame counter on a cineviewer, in a blind manner.[6] We diagnosed MVS by TIMI frame count as 60 counts or more in LAD and 45 or more in LCX.

Statistical Analysis

Continuous variables were expressed as mean ± SD. Comparisons among groups were made by use of 1-way ANOVA followed by post-hoc test with Stat View (SAS Institute, Cary, NC). *P* values less than 0.05 were considered to be statistically significant.

RESULTS

Characteristics of Patients

Depending on the results of the ACh provocation test, the subjects were divided into 4 groups, including no myocardial ischemia (Normal), epicardial spasm alone (ES), microvascular spasm (MVS) alone, and both (ES + MVS) (Table 1). There was a predominance of women in MVS and ES + MVS (Table 1). Current smoking was more prevalent in ES group, but the prevalence of other coronary risk factors was comparable among the 4 groups. Ischemia signs were observed during the ACh provocation test in ES, MVS, and ES + MVS groups but not in the Normal group (Table 1).

Correlation With TIMI Frame Count and Myocardial Ischemia of Microvascular Origin

TIMI frame count was significantly increased in the MVS and ES + MVS groups compared with the Normal or ES group both under control conditions (Fig. 1) and after ACh (Fig. 2) in both left coronary arteries. Importantly, ISDN did not improve TIMI frame count in the MVS or ES + MVS group (Fig. 3).

When all patients were divided into 4 groups by the number of ischemia signs (chest pain, ischemic ECG changes, and myocardial lactate production), 29 patients had no ischemia signs, 10 had 1 sign, 55 had 2 signs, and 37 had all 3 ischemia signs (Fig. 4). TIMI frame count in control CAG was significantly increased in accordance with the number of ischemia signs (Fig. 4). Furthermore, the TIMI frame count in LAD significantly correlated with that in LCX in patients with MVS, suggesting the diffuse impaired coronary microcirculation in the myocardium (Fig. 5).

When MVS was diagnosed by increased TIMI frame count with 60 or more in LAD and 45 or more in LCX, control

TABLE 1. Characteristics of Patients

	Normal	ES	ES + MVS	MVS	*P* Value
n	27	53	16	35	
Age	57.4 ± 14.2	60.7 ± 8.5	59.0 ± 10.9	60.8 ± 9.8	N.S
Sex (male/female)	12/15	35/18	5/11†	10/25††	<0.01
Coronary risk factors					
Hypertension	44%	42%	38%	49%	N.S
Diabetes	7%	19%	6%	11%	N.S
Smoking	30%	51%	19%†	26%†	<0.05
Hypercholesterolemia	19%	40%	44%	31%	N.S
Family history	33%	17%	6%	14%	N.S
Ischemia sign					
Symptom	4%	89%*	94%**	80%**	<0.01
ECG changes	0%	77%**	88%**	74%**	<0.01
Lactate production	4%	36%**	63%**	83%**	<0.01
Lactate extraction ratio	0.13 ± 0.17	0.02 ± 0.33	−0.26 ± 0.44**††	−0.13 ± 0.21*†	<0.01

Continuous variables are expressed as mean ± SD. *$P < 0.05$, **$P < 0.01$ vs. Normal, †$P < 0.05$, ††$P < 0.01$ vs. ES, statistically analyzed by one-way ANOVA followed by post-hoc test.

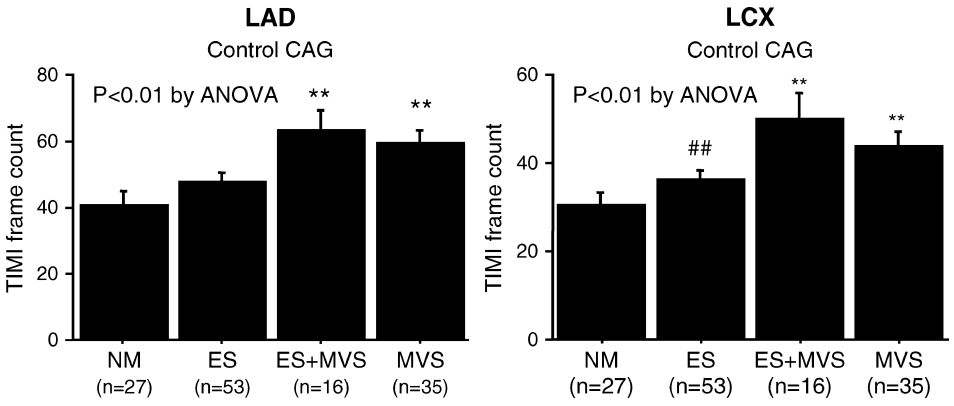

FIGURE 1. TIMI frame count in control coronary arteriograms (CAG) among the 4 groups. TIMI frame count was significantly increased in patients with both epicardial and microvascular spasm (ES + MVS) and MVS alone (MVS) compared with those with no myocardial ischemia (Normal) and epicardial spasm alone (ES) under control conditions in both LAD and LCX (**$P < 0.01$ versus Normal or ES; ##$P < 0.01$ versus Normal).

CAG had a sensitivity of 45% for LAD and 47% for LCX and a specificity of 77% for LAD and 75% for LCX (Fig. 6).

DISCUSSION

The novel findings of the present study were that (1) TIMI frame count, a marker of coronary blood flow, was significantly increased in MVS irrespective of the presence or absence of ES, (2) TIMI frame count was significantly increased in accordance with the number of ischemia signs, and (3) TIMI frame count had an acceptable specificity to diagnose MVS. Thus, the present study suggests that TIMI frame count may reflect the severity of microvascular dysfunction and therefore may be useful to diagnose the disorder. Our group has previously reported that basal coronary tone is elevated in patients with variant angina.[7] Therefore, the combination of basal coronary tone and TIMI frame count may be helpful in diagnosing a patient with ES and/or MVS without performing coronary sinus catheterization or myocardial lactate production measurement. TIMI frame count also has been demonstrated to be useful in detecting the coronary flow changes in patients with stent implantation[8] or the impaired coronary microcirculation in patients who have intracoronary thrombus, impaired flow, and increased burden of coronary atherosclerosis.[9]

The present study also demonstrates that ISDN can reduce symptoms caused by ACh but fails to improve TIMI frame count in patients with MVS. This result suggests that ISDN alone can not effectively ameliorate myocardial ischemia caused by MVS sufficiently because nitrates are great large vessel dilators but not very good at dilating resistance arteries, which is compatible with the previous studies.[10,11] To improve quality of life in patients with MVS, we usually prescribe CCBs, angiotensin-converting enzyme inhibitors, or nicorandil, alone or in combination, with the limited effectiveness.[2]

The precise mechanism of MVS still remains unclear. It has been demonstrated that hypersensitivity to vasoactive substances in MVS is partially mediated by thromboxane A_2[12] and that myocardial ischemia enhances contractile response of coronary arterioles to serotonin, probably through vasoconstrictor prostaglandin release (eg, thromboxane A_2) by upregulated cyclooxygenase (COX)-2.[13] We have recently demonstrated that the Rho/Rho-kinase pathway also plays an important role in the pathogenesis of MVS.[14–16] Therefore, it remains to be examined whether Rho-kinase inhibitor is useful for treating MVS.

Limitations of the Study

Several limitations should be mentioned for the present study. First, we did not directly examine coronary flow velocity using a flow wire technique. However, the validity of TIMI frame count to represent coronary flow velocity has previously been confirmed.[6,8,9,17,18] Second, because we used only ISDN as a vasodilator, we were unable to correlate TIMI

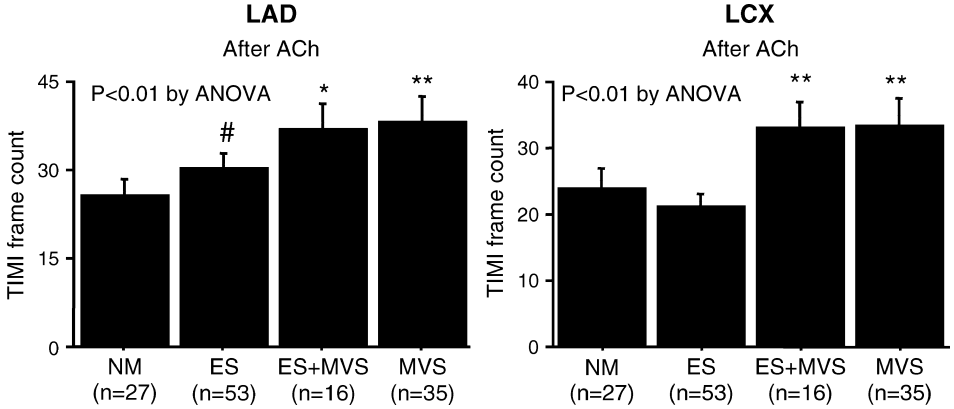

FIGURE 2. TIMI frame count in coronary arteriograms after intracoronary ACh among the 4 groups. TIMI frame count was significantly increased in patients with both epicardial and microvascular spasm (ES + MVS) and MVS alone (MVS), compared with those with no myocardial ischemia (Normal) and epicardial spasm alone (ES) under control conditions and after intracoronary ACh in both LAD and LCX (**$P < 0.01$ versus Normal or ES, *$P < 0.05$ versus Normal or ES, #$P < 0.05$ versus Normal).

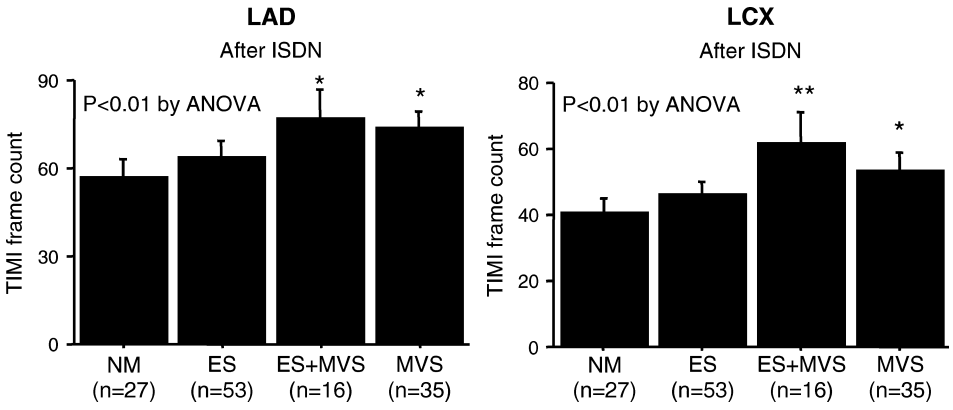

FIGURE 3. The effects of ISDN on TIMI frame count among the 4 groups. Intracoronary administration of ISDN did not improve the increased TIMI frame count in patients with both epicardial and microvascular spasm (ES+MVS) and MVS alone (MVS) (**$P < 0.01$ versus Normal or ES, *$P < 0.05$ versus Normal or ES).

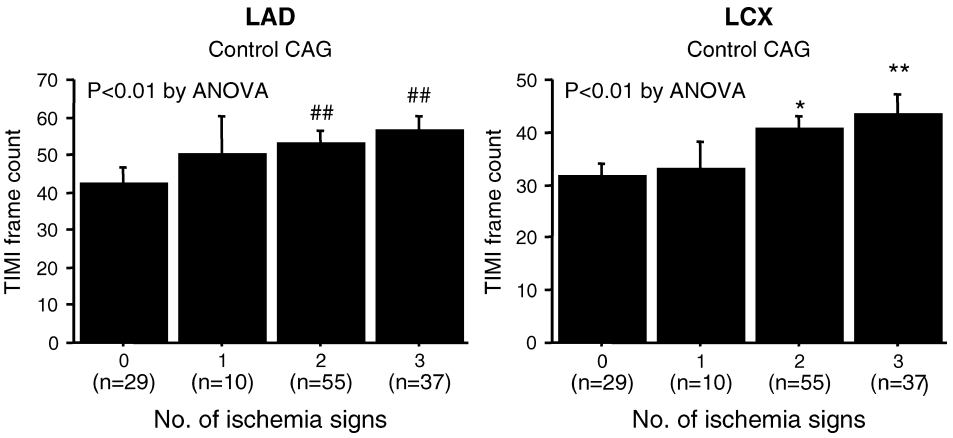

FIGURE 4. TIMI frame count in control coronary arteriograms (CAG) and CAG after ISDN in patients divided according to the number of ischemic signs. TIMI frame count was significantly increased in patients with more ischemic signs of chest pain, ischemic ECG changes, and myocardial lactate production, which was induced by 10 or 30 μg of intracoronary ACh under control conditions but not after intracoronary ISDN in both LAD and LCX (**$P < 0.01$ versus 0 or 1, *$P < 0.05$ versus 0 or 1, ##$P < 0.01$ versus 0, No., number).

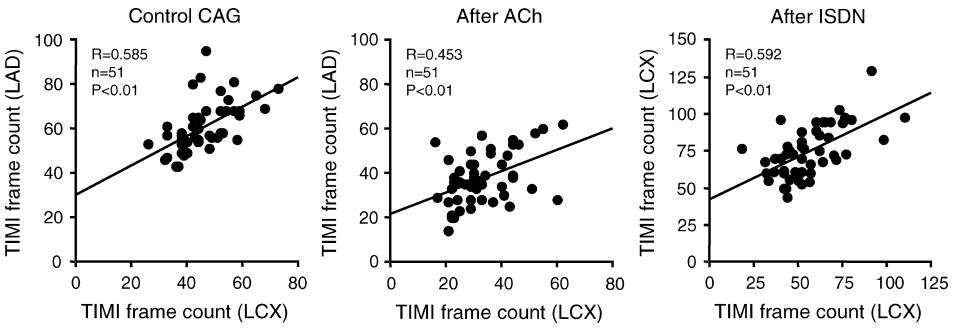

FIGURE 5. Correlations between LAD and LCX in TIMI frame count. TIMI frame count in LAD correlates well to that in LCX in patients with MVS, which suggested that impaired coronary microcirculation might exist in both LAD and LCX areas. CAG, coronary arteriograms.

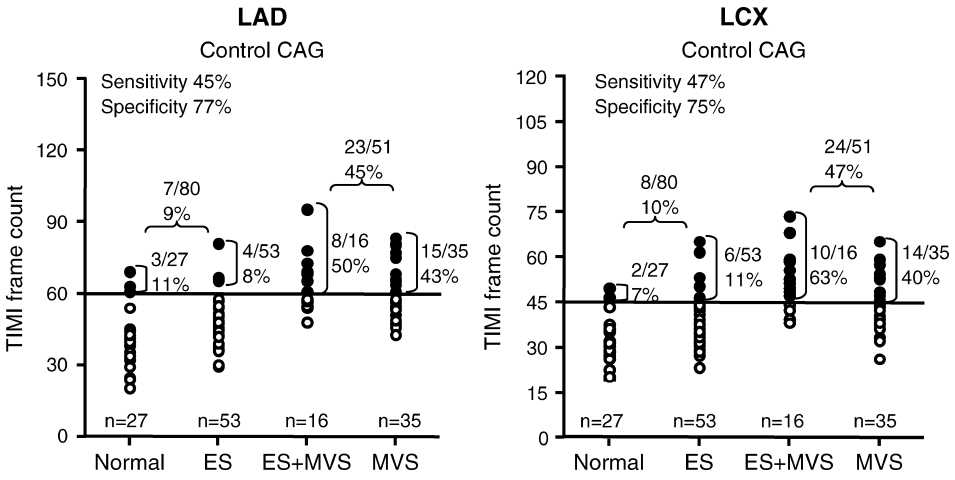

FIGURE 6. Usefulness in diagnosis of microvascular spasm. TIMI frame count of 60 or more in LAD showed a sensitivity of 45% and a specificity of 77% in control coronary arteriograms as a diagnosis of MVS. That of 45 or more in LCX showed a sensitivity of 47% and a specificity of 75%. CAG, coronary arteriograms.

frame count data with those on coronary flow reserve or endothelial function in patients with MVS. Third, because it is difficult to define the severity of microvascular angina, the new noninvasive technique or some marker is required to evaluate the severity of the microvascular circulation in the future. These points remain to be examined in a future study.

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