

# The value of transient ischemic dilation for detecting restenosis after coronary artery revascularization

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**Aim.** Transient ischemic dilation (TID) is a marker of severe coronary artery disease (CAD). We aimed to assess the incremental value of TID in a cohort of patients with known significant CAD who had recurrence of symptoms after revascularization.

**Methods.** We identified in our databases 104 patients who had recent coronary revascularization and recurrence of symptoms. 62 patients had PCI (75 arteries) and 42 patients had CABG (104 arteries). All had follow-up stress SPECT MPI and repeat coronary angiography. Myocardial perfusion findings of ischemia and TID were correlated with presence of significant obstructive CAD ( $\geq 70\%$  stenosis).

**Results.** Follow-up stress Tc-99m Sestamibi SPECT MPI revealed inducible ischemia in 38 patients (36.5%) and TID  $\geq 1.20$  in 49 patients (47%). Subsequent coronary angiography showed significant obstructive CAD in 44 patients (42%). The sensitivity for detecting obstructive CAD was 61% for SPECT MPI alone, but increased significantly to 93% by the addition of TID as a diagnostic criterion ( $P < 0.0001$ ).

**Conclusions.** In this selected patient cohort with prior coronary revascularization, TID is an important marker of obstructive CAD and has incremental value over SPECT MPI alone. (J Nucl Cardiol 2018;25:586–92.)

**Key Words:** Coronary artery disease • coronary revascularization • myocardial perfusion imaging: SPECT • transient ischemic dilation

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### Abbreviations

CAD	Coronary artery disease
CABG	Coronary artery bypass grafting
EF	Ejection fraction
EDV	End-diastolic volume
ESV	End-systolic volume
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
SPECT	Single-photon emission computed tomography
TID	Transient ischemic dilation
Tc-99m	Technetium-99m-
Sestamibi	methoxyisobutylisonitrile

## INTRODUCTION

Stress myocardial perfusion imaging (MPI) with single-photon emission computed tomography (SPECT) is a well-established noninvasive imaging modality for evaluating patients with suspected or known coronary artery disease (CAD). In addition to evaluating regional myocardial perfusion, electrocardiographic gating allows for the assessment of left ventricular (LV) function parameters, i.e., LV ejection fraction (EF).<sup>1,2</sup> Severe stress-induced ischemic LV dysfunction may be detected also on SPECT MPI by nonperfusion markers such as transient ischemic dilation (TID) of the LV. The latter finding is considered another potent marker of severe CAD and predictor of future cardiac events, even when myocardial perfusion appears normal.<sup>3-8</sup> Thus far, TID has been evaluated mainly in patients with suspected CAD and varying prevalence of CAD. The yield of prognostic markers may be affected by clinical characteristics of a patient cohort, e.g., when CAD prevalence is high, the prognostic value of TID might be different compared to a cohort with lower prevalence of CAD.<sup>9</sup>

The aim of the present analysis was to evaluate the diagnostic value of TID in a selected cohort of patients with known significant CAD, recent coronary revascularization, and recurrence of symptoms.

## METHODS

### Patients and Study Design

This is a retrospective data base analysis in two hospitals, the Diskapi Yildirim Training and Research Hospital and the Ankara Training and Research Hospital. The databases contain complete demographic and clinical imaging information on 2316 consecutive patients who were referred for nuclear

cardiology procedures. The databases do not include systematic patient follow-up data. The databases were interrogated using the following search criteria: coronary revascularization within the last 4 years, subsequent ECG-gated SPECT MPI, and repeat coronary angiography within 6 months after the index revascularization. The local ethics committees approved the study protocol.

One hundred and four patients (4%) met the search criteria. The clinical indication for repeat evaluation by SPECT MPI was the recurrence of symptoms after revascularization: exertional chest pain ( $n = 63$ ), significant dyspnea ( $n = 19$ ), or combination of the two symptoms ( $n = 22$ ).

The clinical and angiographic characteristics of 104 patients at the time of the index revascularizations are shown in Table 1. Sixty-eight patients had multivessel significant CAD. Eight patients had prior myocardial infarction. In 62 patients, the index procedure was percutaneous coronary intervention (PCI), and in 42 patients it was coronary artery bypasses grafting (CABG). Of note, 7 of the patients who had PCI and 3 of the patients who had CABG were known to have incomplete revascularization because revascularization was attempted but failed or was not feasible for technical reasons. ECG-gated SPECT MPI was performed  $63 \pm 19$  days after the index coronary revascularization. All patients had SPECT MPI first, followed by repeat coronary angiography.

### Stress Protocols and ECG-Gated SPECT MPI

The patients were clinically stable at the time of stress imaging. They were in fasting state and had abstained from caffeine-containing beverages and food for 24 h, prior to imaging. Nitrates were withheld 6 h before testing, and  $\beta$ -blockers and calcium channel antagonists had been stopped for 24-48 h.

Seventy-one patients performed symptom-limited treadmill exercise using the standard Bruce protocol and 33 patients had dipyridamole vasodilator stress (0.57 mg/kg I.V. over 4 min).

SPECT MPI was performed with Tc-99m Sestamibi using either a 1-day (300-450 MBq for the first injection and 900-1350 MBq for the second injection) or a 2-day (750-1000 MBq for each injection) imaging protocol.<sup>1,2</sup> In order to enhance hepatobiliary radiotracer clearance, the patients were encouraged to drink milk and/or eat a fatty meal.

ECG-gated SPECT MPI was performed in supine position using a dual head gamma camera (ECAM, Siemens, Illinois, USA) equipped with parallel-hole low-energy, high-resolution collimators. The energy window (10%) was centered over 140 keV. A total of 64 planar projections (from 45° right anterior to 45° left posterior) were acquired at 25 s per stop, in  $64 \times 64$  matrix. ECG gating was performed using 16 frames per cardiac cycle.

In order to assure the reliability of stress-rest LV volume ratio calculations, technical acquisition parameters and reconstruction angles were recorded precisely and reproduced for

**Table 1.** Baseline clinical and angiographic characteristics of 104 patients with known CAD

Age ± SD	59.1 ± 9.8
Male/female	75 (72%)/29 (28%)
Diabetes	30 (33%)
Hypertension	76 (73%)
Dyslipidemia	60 (58%)
Smoking past and current	21 (20%)
Family history CAD	54 (52%)
Prior myocardial infarction	8 (8%)
CAD (pts/arteries)	104/179
Vessels with CAD (pts)	
1	36
2	61
3	7
Index revascularization	
PCI	
pts/arteries	62/75
LM	0
LAD	26
RCA	29
LCX	20
Complete revasc (pts/arteries)	55/66
Incomplete revasc (pts/arteries)	7/9
CABG	
pts/arteries	42/104
LM	2
LAD	9
RCA	39
LCX	54
Complete revasc (pts/arteries)	39/101
Incomplete revasc (pts/arteries)	3/3

Number of patients (pts) and arteries are shown. Age in years CABG, coronary artery bypass grafting; CAD, significant obstructive coronary artery disease; PCI, percutaneous coronary intervention; LAD, left anterior descending; LCX, left circumflex; LM, left main; RCA, right coronary artery, Revasc, revascularization, SD, standard deviation

stress and rest imaging. Projection data were reconstructed using the same workstation (Xeleris, GE Healthcare, USA) with filtered back projection and automatic reorientation. Identical filter settings were used regardless of the count density. No attenuation correction was applied.

### SPECT Image Analysis

Computer-automated analysis and semiquantitative visual interpretation were performed using commercially available software (4DM SPECT, INVIA Medical Imaging Solutions, Ann Arbor, Michigan, USA). The following imaging parameters were included in analysis: regional myocardial perfusion, LVEF, and stress-rest LV volume ratio.

Myocardial perfusion was analyzed using the standard 17-segment model.<sup>1</sup> Segmental myocardial radiotracer uptake was assessed semiquantitatively using the standard 5-point scoring system (0 = normal uptake and 4 = absent uptake). Global myocardial radiotracer uptake was expressed as summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS). Defect reversibility (i.e., ischemia) was defined as a SDS ≥ 4. The severity of ischemia was categorized as mild, moderate, and severe (Table 2). LV volumes and LVEF were calculated automatically from stress and at rest images. The lower limit of normal LVEF is 0.50.

### Stress-Rest LV Volume Ratio and TID

Stress-rest LV volume ratio was automatically calculated and displayed using the 4DM SPECT software. The ratio was calculated from ungated SPECT stress and rest LV volumes. Endocardial surface was estimated from smoothed image data using a proprietary edge detection algorithm. LV wall thickness was assumed to be 15 mm. The upper limit of normal for the stress-rest LV volume ratio is 1.12, using the automated 4DM SPECT software for Tc-99m Sestamibi imaging without attenuation correction. The normalcy rate of this value is 97%.<sup>4,10-12</sup> A stress-rest LV volume ratio ≥ 1.12 is abnormal and referred to as transient ischemic dilation or TID. The variability of TID measurement in our own laboratory is <3%.

### Coronary Angiography

Selective left and right coronary angiography was performed using the femoral Judkins technique and Iopromide contrast medium (Ultravist 370, Schering AG, Berlin, Germany). The coronary angiograms were analyzed visually and quantitatively using an automated digital angiography and edge detection system (Axiom Artis QCA system, Siemens, Germany). The reproducibility of this quantitative software has been tested and validated using phantom stenoses with known diameters.<sup>13</sup> Significant obstructive coronary artery disease was defined as ≥50% stenosis in the left main coronary artery and ≥70% stenosis in the other epicardial coronary arteries.

Complete revascularization was defined as successful PCI or CABG of all coronary arteries with significant luminal stenosis. Restenosis at follow-up was defined as significant stenosis of a coronary artery that was treated with PCI or significant stenosis of a venous bypass grafts. New stenosis was defined as a significant luminal stenosis not present on the index coronary angiography.

### Correlation SPECT MPI Findings with Coronary Angiogram

SPECT MPI findings were correlated to specific coronary artery territories using the ASNC/AHA 17-segment model<sup>1</sup>: LAD: segments 1, 2, 7, 8, 13, 14, and 17; RCA: segments 3, 4, 9, 10, and 15; LCX: segments 5, 6, 11, 12, and 16; Left main: at least 75% of LAD and LCX territories.

**Table 2.** Findings on follow-up SPECT MPI and repeat coronary angiography

SPECT MPI	
Normal (SSS = 0)	46 (44)
Abnormal (SSS ≥ 1)	58 (56)
Reversible defects (SDS ≥ 4)	38 (36)
Mild (SDS = 4–8)	4
Moderate (SDS = 9–12)	10
Severe (SDS ≥ 13)	24
Fixed defects (SSS ≥ 1, SDS < 4)	20 (19)
LVEF abnormal (≤0.50)	27 (26)
Stress-rest LV volume ratio normal <1.12	50 (48)
TID (ratio ≥1.12)	54 (52)
TID (optimal cut-off ≥1.20)	49 (47)
Repeat coronary angiography	
Obstructive CAD	44 (42)
New stenosis	23 [13 PCI; 10 CABG]
Restenosis	11 [5 PCI; 6 CABG]
Not revascularized stenosis	10 [7 PCI; 3 CABG]
# Vessels with CAD	
1	20 (19)
2	23 (22)
3	1 (1)
Normal or nonobstructive stenosis	60 (58)

Data show patient numbers (%)

CAD, coronary artery disease; LV, left ventricle; LVEF, left ventricle ejection fraction; SPECT MPI, single-photon emission computed tomography myocardial perfusion imaging; TID transient ischemic dilation

### Statistical Analysis

Statistical analysis was performed using commercially available software for Windows (SPSS software, Version 15.0, SPSS Inc, IL, USA). Continuous and categorical variables were expressed as mean ± SD, numbers, and percentages. Spearman's rho test was used to assess the relationship between the variables that were abnormally distributed or ordinal data. A *P* value <0.05 was considered significant.

Imaging data of patients who exercised and of patients who had pharmacological vasodilation stress were analyzed as one group. Gonzalez et al reported previously that there was no significant difference in TID index using the two stress modalities.<sup>14</sup>

Because the aim of this study was to examine the value of MPI variables to predict the presence of significant CAD on repeat coronary angiography, patients who underwent PCI and CABG were analyzed as one group.

Reversible SPECT MPI defects and TID were compared as predictors of significant CAD, i.e., sensitivity, specificity, positive likelihood ratio (PosLR), positive predictive value (PosPV), negative likelihood ratio (NegLR), negative predictive value (NegPV), and overall accuracy.

Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off point of TID value for identifying obstructive CAD. While changing the threshold for TID, the resulting true positive rate (sensitivity) was plotted against the false positive rate (100-specificity). The

point on the resulting ROC curve closest to the left upper corner represents the optimal cut-off value. Since myocardial perfusion variables (SSS, SDS) are semiquantitative categorical variables (in contrast to TID which is a continuous variable), it is not appropriate to perform ROC curve analysis of these MPI findings.

### RESULTS

SPECT MPI findings at follow-up and on repeat coronary angiography are shown in Table 2.

#### Follow-Up SPECT MPI

On follow-up SPECT MPI, 46 patients (44%) had normal MPI and 58 (56%) had abnormal MPI. Of the patients with abnormal MPI, 38 had reversible myocardial perfusion defects and 20 had fixed defects. Eleven of the fixed defects were most likely caused by diaphragmatic (*n* = 8) or breast (*n* = 3) attenuation. Of the remaining 9 fixed defects, 5 (56%) could be explained by prior myocardial infarction. Of the 38 patients (36.5%) with stress-induced myocardial ischemia, 34 (89%) had either severe or moderate ischemia; only 4 patients had mild ischemia (Table 2).

Abnormal stress-rest LV volume ratio ( $\geq 1.12$ ) or TID was present in 54 patients (52%). Of 38 patients with reversible defects, 30 (79%) patients had TID  $\geq 1.12$ .

### Repeat Coronary Angiography

On repeat coronary angiography ( $22 \pm 7$  days after SPECT imaging), 60 patients had either normal

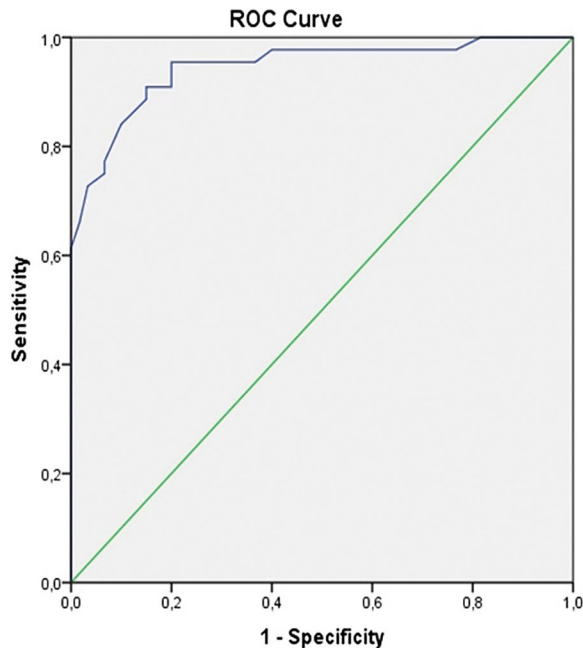
coronary arteries or nonobstructive CAD. 44 patients (42%) had significant obstructive CAD: 11 patients had restenosis, 23 patients had new significant stenoses, and 10 patients had unchanged pre-existing stenoses that were not revascularized. Twenty-four patients had multivessel CAD. Further details are shown in Table 2.

### ROC Curve Analysis of Stress-Rest LV Volume Ratio

Receiver operator curve analysis (Figure 1) of stress-rest LV volume ratio and detection of significant CAD showed an area under the curve of 0.945 (95% CI 0.90-0.99,  $P < 0.01$ ). The optimal cut-off value for detecting significant obstructive CAD was a stress-rest LV volume ratio of 1.20. Using the latter cut-off value, sensitivity was 91% and specificity 85% (Youden's index 0.759).

Stress-rest LV volume ratio was significantly higher in patients with obstructive CAD on follow-up angiography than in patients with normal or nonobstructive CAD ( $1.46 \pm 0.47$  vs  $0.98 \pm 0.15$ ,  $P < 0.001$ ).

Of 38 patients with reversible MPI defects, 27 had significant obstructive angiographic CAD (PosPV = 0.71 (95% CI 0.54-0.84)). Of 49 patients with TID  $\geq 1.20$ , 40 had significant obstructive CAD (PosPV = 0.82 (95% CI: 0.67-0.91)). Of 59 patients who had either ischemia on MPI or TID  $\geq 1.20$ , 41 had significant obstructive CAD (PosPV = 0.69 (95% CI 0.56-0.80)). Table 3 shows the comparative values for detecting significant obstructive angiographic CAD at follow-up angiography using conventional MPI alone, stress-rest LV volume ratio  $\geq 1.20$  alone, or the presence of either of the two parameters. By combining the presence of either abnormal MPI or abnormal LV volume ratio, the diagnostic accuracy and sensitivity for



**Figure 1.** Receiver Operating Characteristic curve analysis of stress-rest LV volume ratios in 104 patients with prior coronary revascularization for detection of obstructive ( $>70\%$ ) coronary artery disease. The area under the curve is 0.945 (95% CI 0.90-0.99),  $P < 0.001$ . The optimal cut-off value for detecting obstructive CAD was 1.20 (Youden's index = 0.7759).

**Table 3.** Detection of significant obstructive CAD by stress-rest MPI alone, TID  $\geq 1.20$  alone, and by combination of these variables

Parameter	MPI alone		TID $\geq 1.20$ alone		Combined	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Sensitivity	0.61	0.46-0.75	0.91	0.82-0.99	0.93	0.86-1.00
Specificity	0.82	0.72-0.92	0.85	0.73-0.93	0.70	0.58-0.82
Accuracy	0.73	0.64-0.82	0.87	0.81-0.93	0.79	0.71-0.87
NegLR	0.47	0.32-0.70	0.11	0.04-0.27	0.10	0.03-0.29
NegPV	0.69	0.62-0.84	0.93	0.82-0.98	0.93	0.81-0.98
PosLR	3.35	1.87-5.99	6.06	3.30-11.15	3.11	2.09-4.61
PosPV	0.71	0.54-0.84	0.82	0.67-0.91	0.69	0.56-0.80

CAD, coronary artery disease; CI, confidence interval; MPI, myocardial perfusion imaging; *n.a.*, not applicable; NegLR, negative likelihood ratio; NegPV, negative predictive value; PosLR, positive likelihood ratio; PosPV, positive predictive value; TID, transient ischemic dilation; Combined = either MPI and/or TID



detecting significant CAD increased significantly to 93% ( $P < 0.001$ ). The PosLR and PosPV remained essentially unchanged, whereas NegLR decreased and NegPV increased indicating the enhanced diagnostic value of negative tests. (Table 3).

## DISCUSSION

This analysis shows that in a selective cohort of patients with prior coronary revascularization, stress-rest LV volume ratio measurements provided incremental diagnostic value over the conventional SPECT MPI defect analysis for detecting significant CAD. Of 44 patients who had significant CAD on repeat coronary angiography, 27 (61%) were detected by reversible myocardial perfusion defects alone. However, when  $TID \geq 1.20$  was added as a diagnostic criterion, 14 additional patients were identified, thereby bringing the total of detected patients to 41 (93%). As shown in Table 3, this increased sensitivity was associated with lower NegLR, high NegPV, and slightly decreased specificity (70%). Thus, TID may be particularly useful because of its high negative predictive value.

TID has since long been recognized as an important marker of severe and extensive CAD. The most likely pathophysiological mechanism for this image pattern is stress-induced subendocardial ischemia, although true LV cavity dilation may also be responsible (6, 7, and 10).

The selective nature of our patient cohort should be appreciated. Although the number of patients who met inclusion criteria for our study was relatively small, the incidence of significant stenoses, i.e., new stenoses and restenoses, was relatively high. In addition, there were pre-existing nonrevascularized stenoses. All patients were symptomatic and most patients with stress-induced ischemia had severe or moderate ischemia. Resting LVEF was abnormal in one-quarter of the patients. The relatively high incidence of TID may be consistent in this context.

The first descriptions of TID were based on subjective visual assessment. However, in clinical practice, the reproducibility of recognizing TID was suboptimal. The calculation of rest-stress LV volume ratio was calculated automatically by a standard component of the 4DM SPECT analysis software.

ROC curve analysis indicated that a TID value of 1.20 was the optimal cut-off for detection of obstructive CAD. Using this value, the prevalence of TID in our patients with obstructive CAD was high (91%) compared to that reported in the literature (about 75%).<sup>6</sup> This high prevalence again points toward a selective patient cohort as mentioned above. All patients had known, although revascularized, CAD. On the initial

angiography, 65% of the study cohort had multivessel disease; on repeat angiography, 24 patients (23%) still had multivessel disease.

On the other hand, TID is not always associated with obstructive CAD and/or localized myocardial perfusion defects. Smelley et al noted in patients without CAD that TID was associated with a hypertensive blood pressure response to exercise. These investigators hypothesized that global subendocardial ischemia might be responsible.<sup>15</sup> Emmett et al observed that TID was associated frequently with left ventricular hypertrophy and also diabetes mellitus; they postulated that microvascular disease and/or impaired coronary flow reserve might be the possible mechanisms.<sup>16</sup>

The sensitivity of MPI defects for detecting significant CAD was relatively low at 61%. This low value could be explained by referral bias. All patients had known severe angiographic CAD, many had multivessel CAD, and all patients had revascularization of at least one vessel. Although all patients were symptomatic, not all angiographic significant-appearing stenoses may have been functionally significant. In addition, 11 fixed myocardial perfusion defects were interpreted as probably attenuation artifacts. Some of these may have represented true ischemia. Finally, the diagnostic yield of MPI may be different in different vascular territories after revascularization.<sup>17</sup>

The aim of the present analysis was to explore whether in patients with high prevalence of CAD image patterns associated with increased risk are still valid. Our analysis indicates that TID remains a robust marker for the presence and absence of severe CAD, even in very selective patients.

## LIMITATIONS OF STUDY

Ours was a retrospective analysis in a highly selective patient cohort. Whether our findings are generally applicable requires verification in a prospective study. Our patients were subjected to two different stress methodologies. True ischemia is more likely to occur in patients performing physical exercise than in patients who underwent pharmacological stress. The basic mechanism of pharmacological stress is the generation of heterogeneity of myocardial blood flow, which is not always ischemic.

Patients who had PCI and CABG were analyzed as one combined group. We were interested in detecting significant obstructive CAD, regardless of the method of revascularization. The end point for TID in our analysis was therefore a diagnostic one: the presence of significant obstructive CAD on coronary angiography. However, TID has been shown also to have prognostic value.<sup>3,7</sup> We did not perform follow-up for occurrence

of subsequent cardiac events. Patients with obstructive CAD at repeat angiography may have received repeat revascularization which should have affected outcome favorably. However, nine patients had TID in the absence of obstructive CAD. Follow-up in these patients for the occurrence of cardiac events also would have been useful.

## CONCLUSION AND NEW KNOWLEDGE

In patients with prior coronary revascularization, TID remains an important and robust marker of significant obstructive CAD and has, even in this selective patient population, incremental value over myocardial perfusion markers alone.

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## Proprietary Interest

*The authors state that they have no proprietary interest in the products named in this article.*

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