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Transient Ischemic Dilation for Coronary Artery Disease in Quantitative analysis of Same-day Sestamibi Myocardial Perfusion SPECT

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Abstract

Background—Transient ischemic dilation (TID) of the left ventricle in Myocardial Perfusion SPECT (MPS) has been shown to be a clinically useful marker of severe coronary artery disease (CAD). However, TID has not been evaluated for 99mTc-sestamibi rest/stress protocols (Mibi-Mibi). We aimed to develop normal limits and evaluate diagnostic power of TID ratio for Mibi-Mibi scans.

Methods—TID ratios were automatically derived from static stress/rest MPS (TID) and gated stress/rest MPS from the end-diastolic phase (TID_{ed}) in 547 patients who underwent Mibi-Mibi scans (215 patients with correlating coronary angiography and 332 patients with low likelihood (LLk) of CAD). Scans were classified as severe (≥ 70% stenosis in proximal left anterior descending artery (pLAD) or left main (LM), or ≥ 90% in ≥ 2 vessels), mild to moderate (≥ 90% stenosis in 1 vessel or 70%-90% in ≥ 1 vessel except pLAD or LM), and normal (<70% stenosis or LLk group). Another classification based on the angiographic Duke prognostic CAD index (DI) was also applied: DI < 30 or LLk group, 30 ≤ DI < 50 and DI ≥ 50.

Results—The upper normal limits were 1.19 for TID and 1.23 for TID_{ed} as established in 259 LLk patients. Both ratios increased with disease severity (P<.0001). Incidence of abnormal TID increased from 2% in normal patients to > 36% in patients with severe CAD. Similarly, when DI was used to classify disease severity, the average ratios showed significant increasing trend with DI increase [P < 0.003]; incidence of abnormal TID also increased with increasing DI. The incidence of abnormal TID in the group with high perfusion scores significantly increased compared to the group with low perfusion scores (stress total perfusion deficit – TPD <3%) (P < .0001). The sensitivity for detecting severe CAD improved for TID when added to mild to moderate perfusion abnormality (3% ≤ TPD < 10%): 71% vs. 64%: P<0.05; and trended to improve for TID_{ed}/ TID_{es}: 69% vs. 64%: P=0.08, while the accuracy remained consistent if abnormal TID was considered as a marker in addition to stress TPD. Similar results were obtained when DI was used for the definition of severe CAD (sensitivity: 76% vs. 66% [P < 0.05] when TID was combined with stress TPD.

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Conclusion—TID ratios obtained from gated or ungated Mibi-Mibi MPS and are useful markers of severe CAD.

Keywords

Single photon emission computed tomography; myocardial perfusion imaging; sestamibi; transient ischemic dilation

INTRODUCTION

Transient Ischemic Dilation (TID) ratio has been clinically acknowledged as a measurement that provides clinically relevant information for the management of patients with coronary artery disease (CAD) (1-9). The change in left ventricular (LV) volume as quantified by TID is probably related to a combination of myocardial and endocardial ischemia (10), although the exact mechanism remains unclear. When incorporated into stress/rest SPECT screening protocols, TID could provide additional information for severe CAD (4, 8). Although the exact significance of quantitatively elevated TID in patients with normal or minimal perfusion abnormality remains unclear and some studies showed that TID had a low prevalence and poor predictive value in the otherwise normal MPI (11–12), the presence of TID in patients with abnormal myocardial perfusion abnormality, such as those in our study, has previously been shown to be associated with extensive and severe coronary artery disease (1, 4, 7, 13, 14), as well as a strong independent predictor of future cardiac events (15, 16). However, different scanning protocols may have different normal limits for TID ratios (8, 9), and these have not been well established. To avoid averaging errors from static images, this study establishes the normal limits not only for ungated SPECT, but also for gated SPECT without attenuation correction using a single isotope ^{99m}Tc -sestamibi tracer. This study also evaluates the Mibi-Mibi TID ratios' incremental diagnostic value in detection of severe and extensive CAD in patients with suspected CAD by fully quantitative analysis.

MATERIALS AND METHODS

Patients

The subjects who were referred to the Nuclear Medicine Department, Sacred Heart Medical Center, Eugene, Oregon, from March 1, 2003 to December 31, 2006 for rest and stress electrocardiography (ECG)-gated MPS were consecutively selected (17). All patients with a prior history of CAD, cardiomyopathy, significant valve disease, left bundle branch block, paced rhythm, and pharmacologic stress testing were excluded. Since the primary goal of this project is to show the diagnostic value of TID for CAD in SPECT using standard ^{99m}Tc -sestamibi rest/stress protocols, only patients with an adequate treadmill stress test (85% of the predicted maximum heart rate) were included. MPS and coronary angiography had to be performed within 60 days without a significant intervening event. The low likelihood (LLk) studies were obtained from patients who performed an adequate treadmill stress test, did not have correlating coronary angiography available, but had < 5% likelihood of CAD using the Diamond and Forrester criteria based on age, sex, symptoms, and ECG response to adequate treadmill stress testing (18). With these selection criteria, 560 studies were identified to form the evaluation group. This population consisted of 2 sub-groups of patients: 215 patients with treadmill MPS and correlative angiography as described above and 332 patients with treadmill MPS and LLk of CAD who were classified as normal. The clinical characteristics for all patients in this study are summarized in Table 1.

Image Acquisition and Reconstruction Protocol

Only summed images without attenuation correction and gated images were considered in this analysis. The details of image acquisition and tomographic reconstruction were previously described (17). In brief, studies were performed by using standard ^{99m}Tc -sestamibi rest/stress protocols. All subjects were imaged at 60 minutes after the administration of Tc-^{99m} sestamibi at rest followed by stress images taken at 15 to 45 minutes after radiopharmaceutical injection during treadmill testing. Tomographic reconstruction was performed by use of the AutoSPECT (Philips Medical Systems). Emission images were automatically corrected for non-uniformity, radioactive decay, and motion during acquisition, and subjected to 3-point spatial smoothing. The alignment of the projection data to the reconstruction matrix was applied to determine the mechanical center of rotation. Data was reconstructed by the filtered back projection method using Butterworth filters with an order of 10 and cutoff of 0.50 for rest MPS, and an order of 5 and cutoff of 0.66 for stress MPS.

Coronary Angiography

Coronary angiography was performed using the standard Judkins method. All coronary angiograms were visually interpreted by experienced cardiologists. All data has been divided into three categories: severe, mild to moderate, and insignificant stenosis based on coronary angiography interpretation (4). Insignificant stenosis is classified as <70% stenosis in all vessels. LLk cases were included as part of the insignificant group. Mild to moderate cases included either 90% stenosis in a single vessel or 70% but <90% stenosis in one or more vessels except stenosis 70% in the proximal left anterior descending artery (pLAD) or the left main (LM). Severe CAD is defined as either 70% stenosis in the pLAD or the LM, or 90% stenosis in two or three vessels. We also applied an alternative classification of severity by previously reported Duke prognostic CAD index (19), which showed prognostic power based on the extent and severity angiography CAD. Similar to Judkins method, we summarized our data into three major categories based on the Duke index (DI): index < 30, 30 ≤ index < 50, and index ≥ 50. All LLk cases were included as part of the first group (index < 30).

Transient ischemic dilation

Standard MPS processing was first performed by the standard Quantitative Perfusion SPECT (QPS)/Quantitative Gated SPECT (QGS) software to derive an ellipsoidal model and contours (20). Then three transient ischemic dilation (TID) ratios derived from static stress/rest MPS and gated stress/rest MPS on the end-diastolic and the end-systolic phases were defined as follows:

$$TID = \frac{Vol_{str_static}}{Vol_{rst_static}}, \quad TID_{ed} = \frac{Vol_{str_ed}}{Vol_{rst_ed}}, \quad \text{and} \quad TID_{es} = \frac{Vol_{str_es}}{Vol_{rst_es}}$$

Where Vol_{str_static} is the endocardial volume for static stress MPS; Vol_{rst_static} is the endocardial volume for static rest MPS; Vol_{str_ed} is the endocardial volume on the end-diastolic phase for gated stress MPS; Vol_{rst_ed} is the endocardial volume on the end-diastolic phase for gated rest MPS; Vol_{str_es} is the endocardial volume on the end-systolic phase for gated stress MPS; Vol_{rst_es} is the endocardial volume on the end-systolic phase for gated rest MPS. The normal limits for both TID ratios were generated using mean ± 2 SD with 259 LLk cases randomly selected from our data (145 subjects with small heart [end-systolic volume in stress image < 30 ml]; 114 cases with ESV ≥ 30 ml) (21).

Previous studies have shown that patients with severe disease had much higher TID ratios compared to patients with mild or moderate disease or insignificant stenosis (4). Therefore, TID ratios' diagnostic values were evaluated in patients with severe stenosis defined as above (Mazzanti et al. (4) and DI). Furthermore, we compared the performance of stress total perfusion deficit (TPD) ($\geq 10\%$) or abnormal TID value alone to the performance of combination of perfusion with TID diagnostic value in the subgroup with mild/moderate perfusion scores ($3\% \leq \text{TPD} < 10\%$) (22).

Statistical Analysis

Continuous variables are denoted as mean $\pm$ standard deviation. The Bonferroni-corrected unpaired t-test was used to compare mean values of continuous variables. The proportion tests were utilized to compare the relation of abnormal TID ratios in different severe stenosis groups and different stress TPD scores. McNemar's test was used to evaluate the incremental performance of TID in the overall cases and patients with angiography. A probability value < 0.05 was considered statistically significant.

RESULTS

Normal limits

The upper normal limit of each TID ratio was defined as the term of its mean plus two standard deviations (SD) generated from 259 stress and rest MPS patients with LLk of CAD randomly selected from our LLk patients on the basis of the random number generator results. The small differences of mean TID ratios between small hearts and regular hearts (0.98 ± 0.12 vs. 0.98 ± 0.09 for TID, 1.05 ± 0.09 vs. 1.07 ± 0.08 for TID_{ed} and 0.99 ± 0.27 vs. 1.03 ± 0.15 for TID_{es}), were not significant ($P > 0.05$). We also obtained TID ratios separately for male ($n = 117$) and female ($n = 142$) patients and found that the differences were not significant (0.96 ± 0.09 vs. 0.99 ± 0.11 for TID, 1.06 ± 0.08 vs. 1.06 ± 0.09 for TID_{ed} and 1.00 ± 0.17 vs. 1.02 ± 0.26 for TID_{es} ; $P > 0.05$). Therefore, the upper abnormal thresholds were established independently of the heart size and gender and generated from all randomly selected LLk patients with 1.19, 1.23 and 1.46 for TID, TID_{ed} and TID_{es} respectively.

Relation between TID ratio and stenosis groups

Table 2 shows that the means of TID ratios were 0.99 ± 0.11 for 401 patients with insignificant stenosis, 1.07 ± 0.13 for 88 patients with moderate disease, and 1.18 ± 0.18 for 58 patients with severe disease. The TID ratios derived from end-diastolic/end-systolic phase showed similar increasing trend among the three severity level groups ($1.06 \pm 0.09/1.04 \pm 0.31$ in insignificant disease group; $1.11 \pm 0.09/1.16 \pm 0.21$ in mild to moderate disease group and $1.17 \pm 0.14/1.32 \pm 0.35$ in severe disease group). All means were significantly different ($P = 0.002$). The relation between the post-stress/rest transient ischemic dilation ratio and stenosis group in all patients is shown in Figure 1. Figure 1A also shows that only 2%, 5% and 4% of patients in the insignificant group have abnormal TID_{ed} (> 1.23), TID_{es} (> 1.46) and TID (> 1.19) (after excluding LLk patients for generating normal limits, similar proportions for abnormal TID_{ed} , TID_{es} and TID in insignificant group were obtained [1%, 9% and 5%]); about 9%, 9% and 15% of the patients in the moderate group have abnormal TID_{ed} , TID_{es} and TID; more than 24% of patients in the severe group have abnormal TID_{ed} and TID.

For groups divided by the Duke prognostic CAD index, the TID ratios' results are also shown in Table 2. Most comparisons between groups were significantly different ($P < 0.003$) with the exception of the difference between the severe disease and moderate group defined by DI (1.22 ± 0.39 vs. 1.34 ± 0.34 ; $P = 0.099$). The relation between the abnormal post-stress/rest transient ischemic dilation ratio and Duke DI categorized group in all

patients is also shown in Figure 1. Figure 1B also shows a similar trend to the relationship between the abnormal TID ratios and stenosis groups: only 3%, 4% and 5% of patients in the insignificant group have abnormal TID_{ed} (1.23), TID_{es} (1.46) and TID (1.19); about 15%, 13% and 17% of the patients in the moderate group have abnormal TID_{ed} , TID_{es} and TID; more than 27% of patients in the severe group have abnormal TID_{ed} , TID_{es} and TID.

Relation between TID ratio and perfusion scores

The relation between the TID ratios and stress TPD in the overall patients is shown in Figure 2. Figure 2 shows that the subgroup with the highest perfusion scores had the biggest percentage of abnormal TID_{ed} and TID. There are significant increases of abnormal TID ratios between the subgroups with low perfusion scores ($TPD < 3\%$), and with high perfusion scores ($TPD \geq 10\%$), ($P < 0.002$). It should be noted that approximately 10% of the LLK patients (34 patients) had $3\% \leq TPD < 10\%$, with only one of these patients also having TID ≥ 1.19 .

Incremental diagnostic value of TID ratios

When abnormal TID (≥ 1.19) was used alone, the sensitivity for severe disease defined by Mazzanti would be 47%. As for using abnormal TID_{ed}/TID_{es} alone, lower sensitivities were obtained (36%/24%). Similar results were obtained for severe DI (56% for TID, 39% for TID_{ed} and 27% for TID_{es}). Figure 3 shows the performance of perfusion quantification alone (TPD), and TPD combined with TID in patients with angiographic correlation and in all patients including LLK patients. For the overall performance, when the TID ratio in the subgroup with mild to moderate TPD ($3\% \leq TPD < 10\%$) was considered (e.g., see an example in Figure 4), the sensitivity for diagnosing patients with severe CAD significantly improved (40% of cases in the patients with severe disease defined by Mazzanti et al. and borderline PD had abnormal TID and 30% of cases had abnormal TID_{ed} and TID_{es}). At the same time, the specificity did not change significantly when the TID ratio was considered and compared to the group without severe CAD. When the TID_{ed} / TID_{es} ratio was added, a similar increase in sensitivity was observed, however, it did not reach statistical significance ($P = 0.08$). When severe Duke Index ($DI \geq 50$) was considered, similar results were obtained (See Figure 5). In addition, the sensitivities for the combination of the TID ratio in the subgroup with mild to moderate TPD ($3\% \leq TPD < 10\%$) and $TPD \geq 10\%$ were significantly higher than for the TID alone ($P = 0.0008$). To show if our criteria for reclassification has resulted in incremental diagnostic improvement, the Receiver Operating Curve (ROC) analysis was performed with one parameter being used in a binary mode (the absolute TID threshold of above 1.19) even though ROC is not optimal due to the need to assume thresholds for one variable.. The ROC for the combination of TPD and TID was 0.7085 versus 0.687 ($P = 0.139$) for TPD alone. Although, the ROC for the combined method was not statistically different than the TPD alone method, this was a noticeable trend.

DISCUSSION

TID ratios of the LV have become an important marker of severe and extensive CAD (4, 8). In this study, we subsequently extended these observations to patients with suspected CAD undergoing single isotope ^{99m}Tc -sestamibi tracer. Both gated and ungated Mibi-Mibi MPS images were used to derive TID ratios. The normal limits of TID ratios were 1.19, 1.23 and 1.46 for static and gated MPS on end-diastolic and end-systolic phase, respectively. The evaluation of incremental diagnostic value of TID ratios showed that the sensitivity for diagnosing the patients with severe CAD by two different definitions improved when abnormal TID was considered as a marker in addition to TPD, without reducing specificity

(among 58 patients with severe disease defined by Mazzanti et al., 40% cases in the patients with severe disease and borderline PD have abnormal TID and 30% cases have abnormal TID_{ed} and TID_{es}). To our knowledge, this is the first study to demonstrate such incremental diagnostic value in a fully quantitative objective manner.

Many previous studies have shown that TID ratio could be considered as a universal high-risk diagnostic marker in myocardial perfusion images (8). However, the upper limits of TID ratios are often different due to different isotopes or protocols (8, 9). Previous studies have shown TID normal limits for dual isotope rest Tl-201/stress Tc-99m (4, 8, 13). The upper normal limit for TID with exercise dual isotope rest Tl-201/stress Tc-99m was defined at 1.22 (4). Other normal limits for TID with rest Tl-201 and same day pharmacologic stress were also defined as 1.27 for dipyridamole, 1.35/1.36 for adenosine, and 1.40 for dobutamine (9). Although one abstract presentation has previously reported TID ratio for similar protocol using rest/exercise stress with ^{99m}Tc-sestamibi tracer (23), the normal values of the TID ratios for the protocol in our study (one day rest/exercise stress with a single isotope ^{99m}Tc-sestamibi tracer, which is currently most commonly applied) has not been previously published in a peer-reviewed literature—we find that the normal limits (1.19 for static and 1.23 for gated images) are similar to the dual isotope protocol (1.23)—despite significant difference in the resting image acquisitions. Previous studies have demonstrated that variations in gender or heart size may result in different TID thresholds (4, 8, 24), which may be due to a technical bias related to smaller absolute left ventricular volumes in females. However, our data did not show significantly different TID thresholds due to heart size or gender. This could be related to use the different protocol or population. Bestetti et al. showed that post-stress end-diastolic left ventricular dilation for 2 day gated stress/rest Tc-99m SPECT was significantly higher in the stunned group compared to the normal group (5). However, the current study used a 1 day rest/stress sestamibi protocol to derive the TID ratios. In addition, previous studies included both suspected CAD patients and patients with a prior CAD history, but our study used only patients with suspected CAD for evaluation, which could affect the evaluation results for abnormal TID ratios. Furthermore, based on the fact that we had used the mean + 2 standard deviations as our normal range, we would expect about ~2% of the normal population to fall outside of this normal range. This will likely explain why 2 to 5% of patients in the insignificant group have abnormal TID_{ed}, TID_{es} and TID, and will lead to overall lower specificity of the combined method based on TID. Moreover, recent studies (25, 26) have shown that there are significant correlations between TID ratios generated from gated images and static perfusion images. Our study used both static and gated SPECT images to generate TID ratios. Similar results from our data have been validated using two definitions of severe CAD, one based on work of Mazzanti et al. (4) and another one based on Duke prognostic CAD index (19). In addition, TID in our study was used to reclassify patients with borderline perfusion defects (3% TPD < 10%) as high risk.

There are several limitations in this study. TID ratios derived from static or gated SPECT images showed significant, but small improvements for diagnosing severe CAD over standard perfusion measures. One reason might be related to the relatively small number of patients in the severe disease group. It is also possible that a more optimal selection of thresholds for the combination of TPD and TID would result in higher diagnostic power. However, a larger study would be required to prove this. In addition, compared to previous studies, our study only included suspected CAD patients. However, these are the patients in which MPS is performed for diagnostic purposes. This study did not evaluate TID ratio's prognostic value. There can be additional prognostic incremental power of TID ratio in patients with suspected or known CAD. LLk patients were combined with cases with coronary angiography in our analysis of diagnostic accuracy. Therefore, the specificity definition differs from that used in standard analysis of data obtained exclusively with

coronary angiography correlation. However, we also report true specificity for the angiography data only. Finally, we did not include adenosine patients in our study. As previously reported, adenosine patients have much higher normal limits for a dual isotope study (9). Therefore, additional study may be needed to explore and evaluate the diagnostic power of TID ratio in adenosine patients using a single isotope ^{99m}Tc -sestamibi tracer.

CONCLUSION

We have established the normal limits for the ungated or gated one day Mibi-Mibi MPS and evaluated performance of TID for the detection of severe CAD. The results suggest that the TID ratios could provide incremental diagnostic information to standard perfusion analysis in fully automated quantitative analysis for the identification of severe and extensive disease in patients with suspected CAD.

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Figure 1.
 Relation between transient ischemic dilation ratio and severity of coronary artery disease.
 Figure 1A: Relation between TID and severe groups defined by Mazzanti study; Figure 1B:
 Relation between TID and severe groups defined by Duke prognostic CAD index.
 Note: * vs. insignificant group or the group with DI < 30: P < 0.05

Figure 2.
Relation between transient ischemic dilation ratio and stress total perfusion deficit (TPD).
Note: * vs. the group with TPD < 3%: $P < 0.05$

Figure 3.

Performance of perfusion alone and perfusion with TID for the severe group defined by Mazzanti study as compared to the group without severe CAD disease. Figure 3A: Results generated from overall patients (N = 547); Figure 3B: Results generated from patients who have angiography (N = 215).

Note: * vs. the group only using TPD $\geq 10\%$ to do evaluation: $P < 0.05$; \$ vs. the group only using TPD $\geq 10\%$ to do evaluation: $P = 0.08$; # specificity did not change when the TID_{es} was considered.

Figure 4.

Example of severe CAD. First column includes static stress images; second column shows static rest images; third column includes gated stress images on the end-diastolic phase; the last column obtains gated rest images on the end-diastolic phase. In each column, first three rows are in short-axis (SAX) orientation followed by horizontal (HLA) and vertical (VLA) long axis orientation images. The static stress images show a small reversible defect in basal lateral wall. The stress TPD was only 5.7%; however, TID, TID_{ED} and TID_{ES} were abnormal at 1.53, 1.38 and 2.36, respectively. Cardiac catheterization confirmed the presence of severe CAD.

Figure 5.

Performance of perfusion alone and perfusion with TID for the severe group defined by the Duke Index as compared to the group without severe CAD disease. Figure 3A: Results generated from overall patients (N = 547); Figure 3B: Results generated from patients who have angiography (N = 215) Note: * vs. the group only using TPD $\geq 10\%$ to do evaluation: $P < 0.05$; \$ vs. the group only using TPD $\geq 10\%$ to do evaluation: $P = 0.08$; # specificity did not change when the TID_{es} was considered.

Table 1

Patient Characteristics.

	LLK (n = 332)	Angio (n = 215)	P value
Age (Mean $\pm$ SD)	52.7 $\pm$ 11.0	62.4 $\pm$ 10.0	P < 0.001
Gender (Female, %)	61%	38%	P < 0.001
BMI ($\geq$ 30 kg/m ² , %)	35%	39%	NS
Diabetes (%)	0%	18%	P < 0.001
Hypertension (%)	38%	59%	P < 0.001
Hypercholesteremia (%)	39%	50%	0.01
Typical Angina (%)	4%	33%	P < 0.001
Atypical angina/no angina (%)	6%	17%	P < 0.001
Dyspnea (%)	11%	10%	NS
Smoke (%)	24%	15%	0.01
Family History (%)	53%	44%	0.04
Ex duration	8.6 $\pm$ 2.4	6.9 $\pm$ 3.9	P < 0.001
Ex HR	158 $\pm$ 15	146 $\pm$ 15	P < 0.001
Ex chest pain (%)	8%	34%	P < 0.001
TPD (Mean $\pm$ SD)	0.9 $\pm$ 1.7	9.9 $\pm$ 10.6	P < 0.001
Ejection fraction (Mean $\pm$ SD)	63.7% $\pm$ 9.2%	62.7% $\pm$ 11.7%	NS

Table 2
TID ratios' results in groups categorized by Mazzanti and Duke prognostic CAD index

	Mazzanti severe groups			Duke prognostic CAD index		
	Insignificant disease (N = 401)	Moderate disease (N = 88)	Severe disease (N = 58)	DI <30 (N = 428)	30 DI < 50 (N = 78)	DI 50 (N = 41)
TID	0.99±0.11	1.07±0.13 [*]	1.18±0.18 ^{*#}	0.99±0.12	1.08±0.14 [*]	1.21±0.18 ^{*#}
TID _{ed}	1.06±0.09	1.11±0.09 [*]	1.17±0.14 ^{*#}	1.06±0.09	1.11±0.10 [*]	1.18±0.15 ^{*#}
TID _{es}	1.04±0.31	1.16±0.21 [*]	1.32±0.35 ^{*#}	1.04±0.28	1.22±0.39 [*]	1.34±0.34 [*]

Note: DI - Duke prognostic CAD index;

^{*} vs. insignificant disease group or the group with DI < 30; p < 0.003;

[#] vs. moderate disease group or the group with 30 DI 50; p < 0.003.