

Transient Ischemic Dilation Ratio in Regadenoson, Single Isotope Gated Single-photon Emission Computed Tomography Myocardial Perfusion Imaging

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Abstract

Single isotope ^{99m}Tc single-photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) is the most commonly used protocol for nuclear stress testing. Transient ischemic dilation of the left ventricle (TID) has been considered a specific marker of severe coronary artery disease (CAD). Recent publications have questioned the clinical utility of TID, specifically with regadenoson as a stressor and 4DM-SPECT software for TID analysis. These findings have not been demonstrated using other imaging packages. The goal of our study was to establish the TID threshold in the identification of Multi-vessel CAD using Quantitative Perfusion SPECT (QPS) software. Included in this study are 190 patients that had undergone regadenoson-stress, same day, single-isotope ^{99m}Tc MPI and had a coronary angiography within a designated 3-month period. QPS (Cedars-Sinai, LA, CA) automated image analysis software was used to calculate TID ratios which were compared across different CAD categories. Coronary angiograms were reviewed to identify both obstructive and nonobstructive CAD. The mean TID for patients with nonobstructive CAD ($n = 91$) was 1.02 ± 0.11 , and the threshold for TID was 1.24. A receiver operating characteristic curve showed that TID had a poor discriminatory capacity to identify MVD (area under the curve 0.58) with a sensitivity of 3% and a specificity of 97%. In our study with regadenoson MPI in a predominantly African-American population, TID was found to be a poor predictor of MVD using QPS software. The reason is unclear but possibly related to the significant decline in the prevalence of severe CAD in the area where our study took place.

Keywords: Coronary artery disease, myocardial perfusion imaging, regadenoson, single photon emission computed tomography, stress test, transient ischemic dilation

Introduction

Transient ischemic dilation (TID) of the left ventricle has been considered to be a specific marker of severe

and extensive coronary artery disease (CAD).^[1-3] Initial studies, with the use of exercise thallium-201, noted that the size of the left ventricle is sometime larger on the immediate poststress image than on the 4 h redistribution image; the phenomenon of which was named "TID of the left ventricle."^[1] Many patients with multivessel CAD have been found to have an abnormal TID, making this

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finding an easily derived and highly specific marker of multivessel critical stenosis with potential important prognostic value.^[1,4] Several mechanisms are considered responsible for TID on nuclear images; these include subendocardial ischemia, temporary systolic dysfunction or myocardial stunning, and/or a true increase in left ventricular (LV) size.^[5] This phenomenon is most often observed after exercise stress,^[1] but it has also been found to be present in pharmacologic stress testing with direct coronary vasodilating agents including dipyridamole, adenosine, and dobutamine.^[1,2,6-10] Regadenoson was the first selective A_{2A} receptor agonist approved by the Food and Drug Administration as a vasodilator stress agent. It has a rapid onset of action, a short duration; being a selective and potent coronary vasodilator with a good safety profile.^[11] Several authors have reported different values for both specificity and sensitivity, as well as different thresholds abnormal TID. This has been done using dipyridamole as a stressor, and, more recently, regadenoson with both, single and dual isotope SPECT.^[2,6,12-14] The abnormal TID thresholds described in the past years range from 1.31 to 1.39, with the prior being calculated using regadenoson as a stressor and single-isotope technetium-99m myocardial perfusion imaging-single photon emission computed tomography (MPI-SPECT) and using 4DM-SPECT (4DM) version 5.1 (INVIA-Ann Arbor, MI, USA) as a software package.^[14] It is important to mention that the TID thresholds in previous studies have been calculated using either the Emory Cardiac Toolbox (ECTb) or 4DM packages. There have been no previous studies involving Quantitative Perfusion SPECT (QPS) package as a calculating software for TID thresholds. In addition, there are considerable differences between automated quantification software packages in determining an appropriate TID ratio for detection of multivessel CAD, with 4DM showing the highest performance, followed by Cedars QPS, and with the lowest performance ECTb.^[15,16] The objective of our study was to determine the relationship between TID and severity of CAD during regadenoson gated SPECT-MPI single isotope study, using the QPS package (Cedars-Sinai, Los Angeles, CA, USA).

Methods

This study was approved by the Institutional Review Board at Albert Einstein Medical Center, Philadelphia, PA. We reviewed the medical records of 2200 patients' who, between January 2013 and March 2015, underwent clinically indicated regadenoson single isotope myocardial perfusion SPECT imaging using ^{99m}Tc sestamibi as a radiotracer. Only subjects who had a coronary angiogram done within 3 months of the stress test were included in this study. Patients with prior history of coronary artery bypass grafting were excluded

from the study. Furthermore, only those patients who had regadenoson as a stress agent were included in the study. Application of such criteria yielded a final sample size of 190 patients. Among this group, TID ratios were obtained and compared in patients with nonobstructive CAD and obstructive CAD, which included single and Multi-vessel CAD.

Single-photon emission computed tomography myocardial perfusion imaging

All subjects underwent 1-day single isotope ^{99m}Tc sestamibi SPECT imaging. The MPI protocol was performed in accordance with the American Society of Nuclear Cardiology guidelines.^[17,18] Rest imaging was performed 45 min after injection of the radiotracer. Pharmacologic stress test was performed with an intravenous injection of 0.4 mg regadenoson, followed by ^{99m}Tc sestamibi injection 25–30 s later.^[19] Stress images were acquired 45 min after the second radiotracer injection. All images were acquired utilizing a Philips BrightView Gamma Camera (Phillips Healthcare, Andover, MA, USA); the camera was compliant with the quality control testing according to the recommendations of the manufacturer and the National Electrical Manufacturers Association recommendations for SPECT instrumentation quality control. Both, rest and stress images were electrocardiogram-ungated. The images were carefully chosen and analyzed by an experienced nuclear cardiologist, assuring that the entire myocardium was included, and the axis angles were correct. A careful analysis of the raw SPECT cine images was performed before the interpretation of the reconstructed MPI study to identify potential sources of artifact in the images. For calculation of TID, we used a commercially available automated program (QPS, Cedars-Sinai, Los Angeles, CA, USA), which estimates three dimensional image volumes from gated or ungated SPECT. The algorithm operates in the three-dimensional space and uses the stress and rest short-axis image sets. After calculation of the endocardial volumes (bounded by the endocardial surface and the valve plane), it derives the TID ratio as the ratio of LV volumes at stress and rest. In addition to TID, the following data were calculated automatically: Summed stress score (SSS), summed rest score, end-systolic volume, end-diastolic volume, and ejection fraction (EF). It is worth to mention that the spatial limits for the production of myocardial slices were meticulously selected in an attempt to eliminate all extracardiac activity; thus reducing the risk of errors by the automated software.^[20]

Coronary angiography

Coronary angiography was performed as indicated by each patient's primary cardiologist. Each of

these procedures was performed and interpreted by well-trained and experienced interventional cardiologists at our institution. Obstructive CAD was defined as $\geq 70\%$ stenosis in any of three major epicardial arteries or $\geq 50\%$ stenosis of the left main coronary artery. Fractional flow reserve calculation was used to evaluate the clinical significance of stenosis of intermediate severity. For the purpose of our study, multivessel CAD was defined as obstructive disease in the left main coronary artery or >1 major epicardial vessels.

Statistics

Data analysis was performed with IBM SPSS Statistics for Mac, Version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to analyze the baseline characteristics of the subjects in the study and cross-tabbed with the TID ratio and also with the degree of CAD found on angiography categorized as nonobstructive CAD, single-vessel disease, or Multivessel CAD (MVD) including triple vessel disease. Analysis of the categorical variables was achieved using ANOVA, Pearson's Chi-Squared and Fisher's exact test for frequencies < 7 ; other variables were analyzed with a two-tailed Student's *t*-test; statistical significance was defined as $P < 0.05$. Logistic regressions, both univariate and multivariate, were used to describe the association between TID and degree of CAD, including MVD, and to calculate appropriate odds ratios (ORs). Regression analysis was used to compare the relationships between the categorical and continuous variables. A receiver operating characteristic (ROC) curve was done to describe the sensitivity and specificity of the TID ratio to predict MVD.

Results

We included 190 subjects who underwent a clinically indicated regadenoson single-isotope MPI SPECT and coronary angiography within 3 months. One hundred and thirteen (59%) were male and the mean age was 62.3 years [standard deviation (SD) 11.9, Table 1]. The overall prevalence of hypertension was 89%, African-Americans had the highest prevalence of 93%, followed by Caucasians with 88%. Diabetes mellitus was present in 53% of the overall population with a prevalence of 56% in African-Americans and 53% in Caucasians [Tables 1 and 2]. The prevalence of nonobstructive CAD in all races was 47% and had a similar prevalence between African-Americans, Caucasians, and Hispanics [Tables 3 and 4]. The prevalence of MVD in all races was 27%, with predominance in African-Americans [Tables 3 and 4]. Among the group of patients with nonobstructive CAD, 41% had a normal MPI, whereas 51% had an abnormal MPI [Table 4]. The incidence normal and abnormal MPI in the group of MVD was 29% and 28%, respectively. A depressed LVEF $< 35\%$ was found in 7% of the patients, predominantly among African-Americans [Table 1]. Furthermore, 17% of the patients were found to have severe perfusion defects on the basis of a SSS > 13 [Table 1].

The mean TID ratio in patients with nonobstructive CAD was 1.02 (SD 0.11), 1.03 (SD 0.09) for single vessel CAD, and 1.06 (SD 0.09) for multivessel CAD [$P = 0.05$, Table 4]. We then determined the abnormal TID ratio threshold after adding 2 SD to the mean TID (1.02, SD 0.11), thus giving a value of 1.24 (after analyzing the population and determining it had a normal Gaussian

Table 1: Demographic characteristics, comorbidities, and myocardial perfusion imaging

	Full sample (n=190)	Normal TID ratio (< 1.24) (n=184)	Abnormal TID ratio (> 1.24) (n=6)	Severe perfusion defects (SSS > 13) (n=34; 17% of total)	Depressed LVEF ($< 35\%$) (n=14; 7% of total)
Age (years) (mean \pm SD)	62.3 (11.9)	62.3 (12.0)	61.3 (7.2)		
Sex, n (%)					
Male	113 (59)	111 (60)	2 (33)	19 (56)	7 (50)
Female	77 (40)	73 (39)	4 (66)	15 (44)	7 (50)
Race					
African-American	135 (71)	130 (71)	5 (83)	25 (73)	11 (79)
White	32 (16)	32 (17)	0 (0)	3 (9)	2 (14)
Hispanic	16 (8)	16 (9)	0 (0)	3 (9)	0 (0)
Other (i.e., Asian)	7 (7)	6 (3)	1 (17)	3 (9)	1 (7)
History, n (%)					
Hypertension	170 (89)	164 (89)	6 (100)	31 (91)	14 (100)
Diabetes mellitus	101 (53)	96 (52)	5 (83)	18 (53)	7 (50)
CAD	72 (62)	69 (37)	3 (50)	21 (62)	9 (64)
Hyperlipidemia	126 (66)	121 (65)	5 (83)	23 (68)	10 (71)
CAD in family	83 (43)	79 (42)	4 (66)	13 (38)	9 (64)
Tobacco use	75 (39)	72 (39)	3 (50)	14 (41)	5 (36)
Obesity (BMI ≥ 30)	97 (51)	95 (51)	2 (33)	15 (44)	5 (36)

TID: Transient ischemic dilation; LVEF: Left ventricular ejection fraction; SSS: Summed stress score; BMI: Body mass index; CAD: Coronary artery disease; SD: Standard deviation

Table 2: Race and prevalence of risk factors for coronary artery disease

	African-American (n=135)	Caucasian (n=32)	Hispanic (n=16)	Other (Asiatic, Islander etc.) (n=7)
Hypertension	126 (93)	28 (88)	11 (69)	5 (71)
Diabetes mellitus	75 (56)	17 (53)	7 (44)	2 (28)
CAD	85 (45)	19 (59)	10 (62)	4 (57)
Hyperlipidemia	89 (66)	25 (78)	7 (44)	5 (71)
CAD in family	58 (43)	17 (53)	6 (36)	2 (29)
Tobacco use	62 (46)	8 (25)	2 (13)	3 (43)
Obesity (BMI ≥30)	65 (48)	19 (59)	10 (63)	3 (43)

BMI: Body mass index; CAD: Coronary artery disease

Table 3: Severity of coronary artery disease and race

	African-American (n=135)	Caucasian (n=32)	Hispanic (n=16)	Other (Asiatic, Islander etc.) (n=7)
CAD				
Nonobstructive	61 (45)	15 (47)	9 (56)	6 (86)
Single-vessel	32 (24)	9 (28)	4 (25)	1 (14)
Multivessel	42 (31)	8 (25)	3 (19)	0 (0)
Triple-vessel disease				
Yes	13 (10)	3 (9)	2 (12)	0 (0)
No	122 (90)	29 (91)	14 (88)	7 (100)
Left main disease				
Yes	2 (1)	5 (16)	1 (6)	0 (0)
No	133 (99)	27 (84)	15 (94)	7 (100)

CAD: Coronary artery disease

Table 4: Severity of coronary artery disease and transient ischemic dilation

	n=190, n (%)	Abnormal MPI (n=131)	Normal MPI (n=59)	Mean TID (SD)	P
CAD					
Nonobstructive	91 (47)	67 (51)	24 (41)	1.02 (0.11)	0.05
Single-vessel	46 (24)	28 (21)	18 (30)	1.03 (0.09)	
Multivessel	53 (27)	36 (28)	17 (29)	1.06 (0.09)	
Triple-vessel disease					
Yes	18 (10)	13 (10)	5 (8)	1.01 (0.07)	0.316
No	172 (90)	118 (90)	54 (92)	1.03 (172)	
Left main disease					
Yes	8 (4)	5 (4)	3 (5)	1.03 (0.10)	0.888
No	182 (96)	126 (96)	56 (95)	1.03 (0.10)	
History of diabetes					
Yes	101 (53)	74 (57)	27 (46)	1.03 (0.11)	0.458
No	89 (48)	57 (43)	32 (54)	1.03 (0.09)	

TID: Transient ischemic dilation; MPI: Myocardial perfusion imaging; SD: Standard deviation; CAD: Coronary artery disease

distribution) [Table 4]. A ROCs curve was done, showing an area under the curve of 0.58, with a confidence interval of 95% (0.499-0.672). In the logistic regression analysis, the OR of TID for prediction of MVD was 1.02 ($P = 0.982$), the OR of hyperlipidemia for prediction of MVD was 2.73 ($P = 0.015$), and the OR of history of

diabetes for prediction of MVD was 1.42 ($P = 0.320$). We found no significant correlation between TID, and the MPI scores and ventricular volumes by Pearson's correlation analysis.

Discussion

TID ratio has been previously studied as a predictor of multivessel CAD using several MPI protocols including thallium, sestamibi, and dual and single isotope SPECT.^[13,14] Katz *et al.* found the threshold for abnormal TID to be 1.39 with a specificity of 95% and a sensitivity of 15% in SPECT MPI with dual isotope.^[13] Golzar *et al.* found the abnormal TID threshold to be 1.31 for single-isotope SPECT MPI using 4DM-SPECT software.^[14] Compared with the TID cutoff proposed by Katz *et al.* for dual-isotope and the one proposed by Golzar *et al.* for single-isotope, our TID cutoff of 1.24 using QPS software for single-isotope (99mTc) is lower. Our proposed TID cutoff, while similar to those previously reported in other stress protocols, did not provide a significant predictive value in the identification of severe or multivessel CAD.^[21] Despite the differences in TID ratios found between patients with low likelihood of CAD and normal MPI, as well as in patients with significant CAD, we did not find any significant clinical correlation. Thus, the TID threshold, we established had no major utility as an identifier of CAD severity. Our outcomes confirm those proposed by Golzar *et al.* who suggested that TID with regadenoson-stress MPI has questionable clinical utility.^[14] These findings could be related to the constant change in CAD prevalence in the state of Pennsylvania, USA, where our study took place, which may include milder clinical presentations of CAD.^[22] Of note, there has also been a notable decrease in the frequency of abnormal SPECT-MPI studies in recent years.^[23-25] These factors may contribute to the finding of limited predictive value of TID thresholds. Furthermore, comorbidities in patients such as hypertension, chronic kidney disease, and diabetes may play an important role, not only as risk factors for CAD but also for increased LV end-diastolic pressures resulting in abnormally high TID values with less significant CAD.^[26] It is important to consider that the majority of our population was African-American in which there is a statistically higher prevalence of CAD, thus giving a minimal representation of other races. Ours is a single-center study, taking place in a geographical area with an increasing decline in the prevalence of significant CAD.^[22] An additional limitation of our study is the exclusive use of one software package. Moreover, our results should be interpreted cautiously and validated by larger multicenter studies given our small sample size. Nevertheless, this is the first study to assess the relevance of TID using the QPS package in this specific protocol.

Conclusion

Recent studies have questioned the additional value of TID to predict the presence of MVD with regadenoson MPI. In our study, with regadenoson MPI in a predominantly African-American population, TID was found to have limited value as a predictor of the existence of MVD based on our analysis using QPS software. The reason is unclear, but possibly related the significant decline in the prevalence of severe CAD in our patient population and select a geographic region (Pennsylvania, USA), where our study took place.

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Conflicts of interest

There are no conflicts of interest.

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