Computer derived transient ischemic dilation ratio for identifying extensive coronary artery disease using a CZT camera and imaging in the upright position

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Background. **Transient ischemic dilation (TID) of the left ventricle (LV) has not been validated as a marker of extensive coronary artery disease (CAD) for studies using a cadmium-zinc-telluride (CZT) camera with upright imaging.**

Methods. **TID ratios were obtained from upright stress and rest images on a CZT camera. Separate cut-off values were determined for exercise and for regadenoson stress. The cutoffs were then applied to 28 patients with extensive CAD and 101 patients without extensive CAD.**

Results. **With treadmill exercise, an upright TID ratio ≥1.16 provided a positive predictive value of 50% and a negative predictive value of 85.4% for the identification of extensive CAD. In the regadenoson group, an upright TID ratio of 1.29 provided a positive predictive value of 20% and a negative predictive value of 75.9%. Although not an independent predictor of extensive CAD in all subjects, in subjects with a normal upright LVEF, it provided a predictive value by receiver operating characteristics comparable to the SSS.**

Conclusions. **Increased upright TID measurements on a CZT camera are associated with extensive CAD. The upright TID measurements can serve in an adjunctive role to SSS, and may be most effective in patients with a normal upright exercise LVEF. (J Nucl Cardiol 2017;24:1702–8.)**

Key Words: Cadmium-zinc-telluride • myocardial perfusion imaging: SPECT • transient • ischemic dilation (TID) • coronary artery disease

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Abbreviations	
AUC	Area under the curve
CABG	Coronary artery bypass surgery
CAD	Coronary artery disease
CZT	Cadmium-zinc-telluride
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MPI	Myocardial perfusion imaging
PCI	Percutaneous coronary intervention
SPECT	Single-photon emission computerized tomography
SSS	Summed stress score
TID	Transient ischemic dilation

See related editorial, pp. 1709–1711

BACKGROUND

Original ArticleTransient ischemic dilation (TID) of the left ventricle (LV) during stress and rest myocardial perfusion imaging (MPI) refers to an imaging pattern in which the LV cavity appears larger on the stress images compared to those at rest without a significant difference in epicardial ventricular size.[1] Hypothetical mechanisms to explain the presence of TID include: diffuse subendocardial hypoperfusion, post-stress ''myocardial stunning,'' and decreased LV function with resultant elevated end-systolic volume.[2–5] TID has proven to be a useful diagnostic and prognostic marker of severe and extensive CAD in a variety of patient populations and testing modalities.[2,6–11] TID is associated with a poor prognosis even in the presence of normal MPI in patients with diabetes and LV hypertrophy.[12–14] Despite its widespread acceptance and use, a recent study has questioned the utility of TID when used with regadenoson SPECT MPI.[15]

The cut-off value for a ''significant'' TID ratio varies depending on the stress modality, imaging protocol, and radioisotope used. To date, the authors are aware of no published study identifying a significant cut-off value for TID for upright imaging using the recently introduced dedicated cardiac cameras with solid-state CZT (cadmium-zinc-telluride) detectors. Various studies have validated CZT SPECT MPI in comparison with conventional SPECT, and with coronary angiography.[16–18] In this study, we investigated a threshold value for the TID ratio using upright imaging on a CZT SPECT camera and the capability of the upright TID ratio to differentiate extensive CAD from non-extensive CAD.

METHOD

Study Population

The medical records of 740 patients who underwent either exercise or pharmacologic (regadenoson) SPECT MPI for clinical indications from November 2013 to June 2014 were reviewed. From this cohort, 140 subjects underwent coronary angiography within three months of the stress MPI and were included in the present study, regardless of any past history of coronary revascularization by PCI or CABG. A control group of ''exercise normals'' consisted of 48 subjects with <5% pretest probability of CAD[19] and a normal SPECT MPI study. This was a different group of normal subjects, distinct from the group whose studies had been used to create the locally derived normal MPI SPECT database. A separate set of 14 ''pharmacologic normals'' was identified by the combination of (1) no history of CAD or documented non-ischemic cardiomyopathy, (2) no angiographic coronary artery stenosis >30% luminal diameter stenosis, (3) a summed stress score (SSS) of 0, and (4) an end-systolic volume $\geq$20 mL^2. This study was approved by the Institutional Review Board of the University of Cincinnati as a retrospective data review and was exempt from informed consent.

Myocardial Perfusion SPECT Imaging

Patients were instructed not to use caffeinated beverages for 12 hours prior to testing. Beta-blockers were withheld for 24 to 48 hours prior to testing if approval to do so was granted by the referring physician. Stress imaging was performed on a treadmill according to the Bruce protocol and/or using pharmacologic stress with regadenoson 0.4 mg.

Stress and rest imaging were performed in the upright position with additional stress images acquired in the supine position. Images were acquired on a D-SPECT CZT dedicated cardiac camera (Spectrum Dynamics Inc., Palo Alto, CA). Upright imaging was performed with the imaging chair at a 65°-70° angle. Breast and/or abdominal binders were used as appropriate to improve image quality. Stress images were acquired for at least 3 minutes at 30-45 minutes following injection of 30-40 mCi of technetium-99 m tetrofosmin. Rest images were acquired for 3-11 minutes based on body weight at 60 minutes following injection of 10-13 mCi of technetium-99 m tetrofosmin.

SPECT images were processed with iterative reconstruction (ordered subset expectation maximization) on a Spectrum Dynamics Cedars View processing station. Physician review and interpretation of the images were accomplished with the Corridor4DM SPECT software (Invia Medical Imaging Solutions, Ann Arbor, Michigan) in blinded fashion without the knowledge of test indication or patients' clinical data, except gender, height, and weight. Close attention was provided by the nuclear medicine technologist in positioning the base and apex limits to assure the congruence of stress and rest limits. A single additional adjustment was made by the interpreting physician if needed. SSS was recorded from upright and supine positions, summed rest score upright only, upright summed difference score, and average SSS from the average of the upright and

supine stress images. TID ratio from the ungated images, rest, and exercise LVEF were automatically calculated by the 4DM SPECT software.

Coronary Angiography

Patients underwent coronary angiography as part of the evaluation for CAD. All the angiography films were blinded for patient's age, gender, past medical history, presenting symptoms, and stress MPI results. Extensive CAD was defined as an angiographic lesion either ≥50% in the left main, ≥70% in the proximal left anterior descending (LAD) or ≥70% in any two or three epicardial coronary arteries[2,10,11].

Statistical Analysis

Continuous variables were described using mean and standard deviation (SD) while categorical data were described using frequency and proportion. Student's *t* test was used to determine significant difference between samples for quantitative variables while Fisher's exact test was used for categorical variables. The unadjusted logistic regression analysis was carried out to determine factors associated with extensive CAD. The multivariable logistic regression analysis was carried out to determine predictors for extensive CAD. The diagnostic performance of the TID ratio in relation to extensive CAD was summarized by receiver operating characteristics (ROC) using the area under the curve (AUC) with 95% confidence intervals (CI). A TID ratio 2SD above the mean for each normal group was used to define separately a cutoff for the prediction of extensive CAD in the exercise and pharmacologic stress study groups. Stepwise multivariable logistic regression was performed for determining adjusted associations. The results of regression analysis were summarized using odds ratio (OR) along with 95% CI and *P* values. *P* values <5% were considered significant. The best predictive model was selected based on the highest AUC for the model. ROC curves were constructed for considered tests. All analyses were performed using STATA 12.1.

RESULTS

Characteristics of the 48 exercise normals and the 14 pharmacologic normals are shown in Table 1. Hypertension, beta-blocker use, family history of CAD, and larger TID ratio were more frequent in the pharmacologic controls.

Twenty-eight patients (14.7%) were documented to have extensive CAD and 101 study patients did not. By the univariate analysis, patients with extensive CAD (Table 2) were significantly more likely to be using a beta-blocker, to be dyslipidemic, to have a known history of CAD and/or coronary revascularization, to have undergone pharmacologic stress, and to have a lower stress and rest LVEF. Each of the summed stress scores, summed rest score, summed difference score, and averaged SSS was significantly associated with extensive CAD.

The TID mean ± SD was 0.92 ± 0.12 for exercise controls, 1.03 ± 0.13 for pharmacologic controls, 1.02 ± 0.15 for patients without extensive CAD, and 1.06 ± 0.12 for patients with extensive CAD. The cutoff for an abnormal exercise TID threshold was determined to be ≥1.16, using the mean + 2SD from the exercise controls. An exercise TID cut off of ≥1.16 separated patients with extensive CAD from patients without extensive CAD with a sensitivity of 25%, specificity 94.6%, positive predictive value 50%, and negative predictive value 85.4%. The cutoff for an abnormal pharmacologic TID threshold was determined to be ≥1.29, using the mean + 2SD from the pharmacologic normal subjects. A pharmacologic TID cut off of ≥1.29 separated patients with extensive CAD from patients without extensive CAD with a sensitivity of 5%, specificity 93.8%, positive predictive value 20%, and negative predictive value 75.9%.

The multivariable logistic regression analysis (Table 3) showed hypertension, known history of CAD, history of CABG, resting LVEF, and exercise LVEF to be associated with extensive CAD. After excluding the history of CAD and coronary revascularization, hyperlipidemia (OR: 4.2, 95% CI 1.4-12.9, $P = 0.012$) and upright exercise LVEF (OR 0.95, 95% CI 0.91-0.98, $P = 0.003$) remained significantly associated with extensive CAD. The average SSS was the most predictive of the 5 summed scores analyzed (AUC 0.0.69, 95% CI 0.58-0.80). Average SSS was independently predictive of extensive CAD only after subjects with a resting upright LVEF <50% were excluded. For the full study population, TID was not an independent predictor of extensive CAD.

Individual and combined model performance of TID, average SSS, and upright stress LVEF are shown in Table 4 and Figure 1. The combined model of average SSS and upright stress LVEF provided best predictive ability for extensive CAD (AUC = 0.732) followed by a model with TID and upright stress LVEF (AUC = 0.706). The given equations in Table 4 can be used for predicting likelihood of extensive CAD compared with no extensive CAD. When patients with a normal exercise LVEF were considered, average SSS and TID provided comparable prediction of extensive CAD.

An infrequent but clinically very important issue is the identification of patients who may have extensive CAD with no regional perfusion abnormality (i.e., ''balanced ischemia''). In the present population, no patient with extensive CAD and a normal (<4) summed stress score had a TID ratio ≥1.16.

Table 1. Distributions of cofactors of normal subjects

Characteristics	Exercise normals, N = 48	Pharmacologic Normals, N = 14	*P* value
Age (years)	53.3 ± 6.4	50.9 ± 6.8	0.221
BMI (Kg/m^2)	29.4 ± 5.9	31.2 ± 8.3	0.353
Male	16 (33)	6 (43)	0.539
Diabetes	7 (15)	6 (43)	0.056
Hypertension	20 (42)	12 (86)	0.005
Smoking	17 (35)	8 (57)	0.216
Beta-blocker use	5 (10)	9 (64)	0.000
Dyslipidemia	6 (13)	4 (29)	0.213
Family history of CAD	17 (35)	11 (79)	0.006
CAD, PCI, CABG, NICM	0 (0)	0 (0)	
TID	0.92 ± 0.12	1.03 ± 0.13	0.006
Stress ejection fraction (%)	60.7 ± 7.2	57.4 ± 9.00	0.153
Rest ejection fraction (%)	59.0 ± 8	57.9 ± 11.4	0.678
Change in LVEF	0.02 ± 0.06	−0.01 ± 0.06	0.237

BMI, body mass index; *CAD*, coronary artery disease; *PCI*, percutaneous coronary, intervention; *CABG*, coronary artery bypass surgery; *NICM*, non-ischemic cardiomyopathy; *TID*, transient ischemic dilation; *LVEF*, left ventricular ejection fraction; *OR*, odds ratio; *CI*, confidence interval

Table 2. Clinical characteristics, stress test variables, and univariate predictors of extensive CAD compared to no extensive CAD

Characteristics	No Ext CAD	Ext CAD	OR	95% CI		*P* value
Age (years)	59.2 ± 9.3	60.3 ± 8.6	1.01	0.97	1.06	0.558
BMI (Kg/m^2)	33.7 ± 25.7	30.5 ± 5.2	0.98	0.92	1.05	0.556
Male	59 (58)	20 (71)	1.78	0.72	4.42	0.215
Diabetes	41 (41)	13 (46)	1.27	0.54	2.94	0.580
Hypertension	80 (79)	27 (96)	7.09	0.91	55.2	0.062
Smoking	52 (52)	18 (64)	1.70	0.71	4.03	0.232
Beta-blocker use	72 (71)	26 (93)	5.24	1.17	23.5	0.031
Dyslipidemia	58 (57)	23 (82)	3.41	1.20	9.69	0.021
Family history of CAD	44 (44)	17 (61)	1.97	0.84	4.63	0.121
CAD	49 (49)	25 (89)	8.84	2.51	31.2	0.001
History of PCI	33 (33)	16 (57)	2.75	1.17	6.47	0.021
History of CABG	7 (7)	12 (43)	10.1	3.45	29.4	0.000
NICM	10 (10)	1 (4)	0.34	0.04	2.75	0.310
Pharmacologic stress	64 (64)	20 (71)	1.45	0.58	3.61	0.430
TID	1.02 ± 0.15	1.06 ± 0.12	8.81	0.48	160	0.142
Upright SSS	4.2 ± 4.5	7.2 ± 5.8	1.12	1.03	1.21	0.007
Supine SSS	4.6 ± 4.4	7.7 ± 5.2	1.13	1.04	1.24	0.004
Upright SRS	1.7 ± 2.7	3.3 ± 3.9	1.13	1.00	1.27	0.021
Summed difference score	2.5 ± 3.05	4.0 ± 3.8	1.14	1.04	1.25	0.048
Average SSS	4.4 ± 4.27	7.5 ± 5.0	1.16	1.02	1.32	0.004
Exercise LVEF (%)	53.4 ± 13.5	44.3 ± 12.5	0.95	0.92	0.98	0.003
Rest LVEF (%)	53.9 ± 13.5	46.9 ± 13.2	0.96	0.93	0.99	0.020
Change in LVEF	0 ± 0.08	−0.03 ± 0.06	0.02	0.00	6.39	0.191

Ext, extensive; *BMI*, body mass index; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass surgery; *NICM*, non-ischemic cardiomyopathy; *TID,* transient ischemic dilation; *LVEF*, left ventricular ejection fraction; *SSS*, summed stress score; *SRS*, summed rest score; *OR*, odds ratio; *CI*, confidence interval

Table 3. Predictors of extensive CAD compared with no extensive CAD

Characteristics	OR	95% CI		*P* value
Hypertension	12.9	1.23	134	0.033
Rest ejection fraction (%)	1.10	1.01	1.19	0.03
History of CABG	8.60	2.25	32.9	0.002
CAD	11.7	2.40	56.5	0.002
Stress ejection fraction (%)	0.86	0.78	0.94	0.001

CABG, coronary artery bypass surgery; *CAD*, coronary artery disease; *OR*, odds ratio; *CI*, confidence interval

DISCUSSION

TID has long been used to identify patients with multi-vessel or extensive CAD, who are at increased risk of adverse cardiovascular events. Abnormal TID ratios have been published previously using specific camera and testing protocols[8]. However, to date, no validated TID ratio cutoff has been published for upright imaging on a CZT camera. As in previous studies, the present study defined an abnormal treadmill exercise only TID cutoff based on a value that is 2SD above the mean TID of a population of subjects with a very low pretest likelihood that coronary disease is present[7,10,11,14,15]. The resultant TID ratio cutoff in the present study was 1.16, which provided a positive predictive value of 50% and a negative predictive value of 85.4% in differentiating patients with extensive CAD from those without. As noted previously[15], very few subjects who are referred for pharmacologic stress MPI have a pretest likelihood of CAD <5%. Consistent with a previous report[15], pharmacologic stress control subjects were identified for the present study based on a low likelihood of CAD from historical and clinical variables. Thus, the pharmacologic normal group for the present study was identified by a SSS of 0, no known coronary disease or history of revascularization, no documented lesion >30% by subsequent coronary angiography, no documented non-ischemic cardiomyopathy, and no end-systolic volume less than 20 mL. A TID cut-off value of 1.29 for subjects who underwent pharmacologic stress was based on a value 2SD above the mean of the 14 pharmacologic controls. A cutoff of 1.29 yielded a positive predictive value of 20% and a negative predictive value of 75.9% for the identification of extensive CAD.

The SSS is an index that reflects both extent and severity of CAD. In the present study the optimal SSS for identifying extensive CAD was the average of the upright and supine SSS; however, the upright SSS alone was also predictive. The SSS has served as a marker for extensive angiographic CAD and for high risk for cardiac death or myocardial infarction in previously published studies[20,21]. On the multivariable analysis, the average SSS was an independent predictor of extensive CAD, but only after the clinical variables, known CAD, PCI, and CABG, and an exercise LVEF <50% were removed. By the multivariable analysis, the TID ratio was not an independent predictor of extensive CAD.

The TID ratio is automatically computed by most MPI analysis programs and serves in an adjunctive role for the identification of extensive CAD. This adjunctive

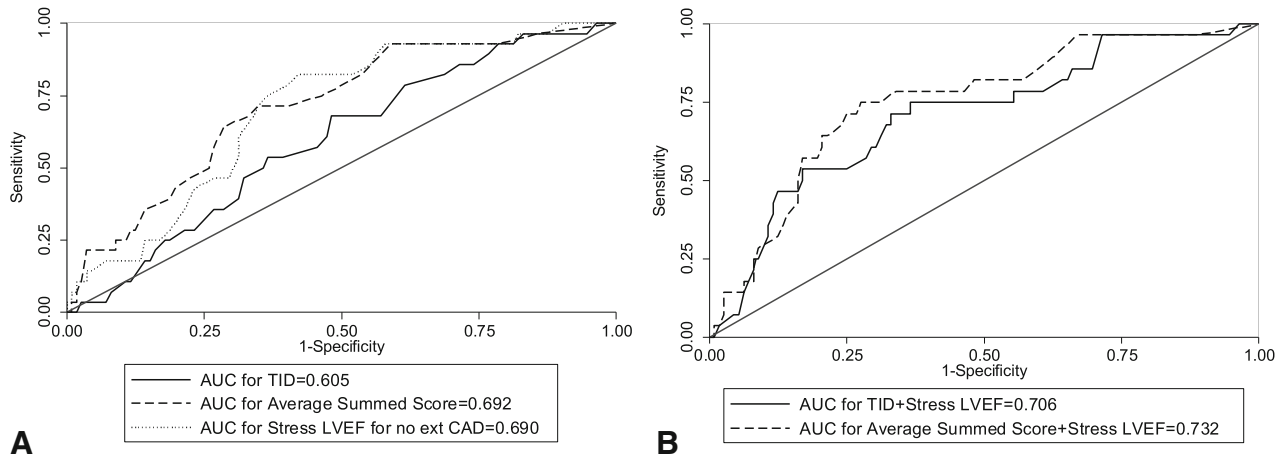

Figure 1. (**A**) Receiver operating characteristics (ROC) curves for prediction of extensive coronary artery disease for TID, average SSS, and upright exercise left ventricular ejection fraction. (**B**) Receiver operating characteristics (ROC) curves for the prediction of extensive coronary artery disease for the combinations of TID and exercise left ventricular ejection fraction.

Table 4. Individual and combined performance of TID, average SSS, and stress LVEF

Characteristics	AUC	95% CI	
TID	0.605	0.493	0.716
Average SSS	0.692	0.584	0.799
Stress LVEF	0.690	0.589	0.792
TID + stress LVEF (≥50%)*	0.706	0.597	0.815
Average SSS + stress LVEF (≥50%)$^{+}$	0.732	0.628	0.836

TID, transient ischemic dilation; *SSS*, summed stress score; *LVEF*, left ventricular ejection fraction; *AUC*, area under the curve; *CI*, confidence interval
* Probability of extensive CAD = −2.39 + 1.67 × TID − 1.40 × Stress LVEF (≥50%)
$^{+}$ Probability of extensive CAD = −1.30 + 0.09 × Average SSS − 1.16 × Stress LVEF (≥50%); Use "1" for patient with LVEF ≥50% otherwise "0" in the equations

role reflects limited sensitivity of the TID ratio for the identification of extensive CAD, varying from 15% to 28% in published series when severe coronary artery stenosis is defined as a ≥70% luminal narrowing[9,11]. When a more conservative 90% stenosis is required to define a significant stenosis to extensive or multi-vessel CAD, higher sensitivity of the TID ratio has been described[7]. In the present study a significant stenosis was defined as 70% and the prospectively defined TID ratio of 1.16 also provided the optimal combination of sensitivity and specificity (i.e., diagnostic accuracy) by the ROC analysis (data not shown). Attempts to use a lower TID cutoff to improve sensitivity are limited by a resultant decline in specificity, as increasing TID has been shown in response to hypertension[13,22], diabetes[13,14], gender[23], small left ventricular volumes[2], change in heart rate from rest to post-stress image acquisition[24], and patient motion[25].

Compared to the mean TID ratio with exercise stress testing, the mean TID ratio with pharmacologic stress testing was higher for both patients with and without extensive CAD, which is in agreement with previously published findings[8]. Overall exercise TID was found to be superior to pharmacologic TID for the separation of patients with vs without extensive CAD.

Although an upright TID ratio was automatically provided by the commercial software used in the present study, little attention in the literature has been addressed to the role of an upright TID ratio in identifying extensive CAD. Past studies with first pass angiocardiography documented that left ventricular volumes in the upright position differ in the response to exercise between subjects with CAD and normal subjects[26]. In the present study, an upright TID ratio cutoff was identified that separated patients with extensive CAD from normal subjects and patients with less extensive disease; however, much of the information from the TID ratio for the identification of patients with extensive CAD was also available from historical and clinical variables and from the SSS.

Golzar and associates[15] recently described limited utility of the TID ratio for separating patients with extensive vs non-extensive CAD using regadenoson coronary vasodilation, a conventional SPECT camera system, and supine imaging. They questioned the utility of the TID ratio for the assessment of CAD severity and extent in an era of decreasing prevalence of extensive CAD. Findings of the present study are in agreement with that report.

Findings from the present study are limited to patients from a single center, the upright position, and using a CZT camera with analysis on a single software system. The TID ratio cutoff in the present study is not intended to apply to images acquired on a CZT camera using the supine position. In addition, as is common practice to reduce interference with myocardial images from adjacent activity in digestive organs[27], adjunctive exercise was added to pharmacologic stress in patients who were able to perform low-level treadmill exercise.

NEW KNOWLEDGE GAINED

The present study provides validation for exercise and pharmacologic stress cutoff TID ratios for the identification of patients with vs without extensive CAD as determined by upright imaging on a CZT cardiac camera.

CONCLUSION

Increased upright TID measurements on a CZT camera are associated with extensive CAD. The upright TID measurements can serve in an adjunctive role to SSS, and may be most effective in patients with a normal upright exercise LVEF.

Disclosure

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