Journal of the American College of Cardiology
© 2003 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 42, No. 10, 2003
ISSN 0735-1097/03/$30.00
doi:10.1016/j.jacc.2003.07.010

Cardiac Imaging

Transient Ischemic Dilation Ratio of the Left Ventricle Is a Significant Predictor of Future Cardiac Events in Patients With Otherwise Normal Myocardial Perfusion SPECT

Aiden Abidov, MD, PHD,* Jeroen J. Bax, MD,† Sean W. Hayes, MD,*
Rory Hachamovitch, MD, MSC, FACC,‡ Ishac Cohen, PHD,* James Gerlach, CNMT,*
Xingping Kang, MD,* John D. Friedman, MD, FACC,* Guido Germano, PHD, FACC,*
Daniel S. Berman, MD, FACC*

Los Angeles, California; and Leiden, the Netherlands

OBJECTIVES This study evaluated the prognostic value of transient ischemic dilation (TID) of the left ventricle (LV) in patients with normal stress myocardial perfusion single photon emission computed tomography (MPS).

BACKGROUND The prognostic value of TID in patients with an otherwise normal MPS has not been defined.

METHODS We identified 1,560 patients who had normal stress MPS (436 vasodilator and 1,124 exercise stress), and no rest LV enlargement (Population 1) and followed up for 2.30 ± 0.67 years for hard events (HE) (cardiac death or myocardial infarction) and soft events (SE) (revascularization). Prediction of first HE or SE (total events [TE]) was evaluated by multivariable Cox analysis, which was also applied to a broader group of 2,037 patients (including patients with minimal defects (Population 2).

RESULTS In Population 1, there were 13 HE, 36 SE, and 42 TE. Patients in the highest TID quartile (TID ≥1.21) had a higher TE rate than others, regardless of stress type. By multivariable analysis, highest TID quartile was predictive of TE ($p = 0.008$). Other independent predictors of TE were age, typical angina, and diabetes. In Population 2, TID was also predictive of TE.

CONCLUSIONS An entirely normal stress MPS study does not always imply an excellent prognosis. In patients with otherwise normal MPS, TID is an independent and incremental prognostic marker of TE even after significant clinical variables—age, typical angina, and diabetes—are accounted for. When TID is present, caution in making low-risk prognostic statements may be warranted, especially in patients with typical angina, the elderly, and diabetics. Our findings also appear to apply to the broader population of "normal" MPS, which included patients with minimal perfusion defects. (J Am Coll Cardiol 2003;42:1818–25) © 2003 by the American College of Cardiology Foundation

Patients with extensive perfusion defects on myocardial perfusion single photon emission computed tomography (MPS) are at high risk for hard cardiac events (HE) (cardiac death [CD] or myocardial infarction [MI]) (1–7) and may benefit from cardiac catheterization with possible revascularization (8,9). While patients with normal MPS have an excellent prognosis (6,10,11), a small proportion develop future HE. Prior studies have shown that advanced age, diabetes, and known coronary artery disease (CAD) (prior MI or revascularization) are predictors of an HE rate in patients with normal MPS (12). Transient ischemic dilation (TID) of the left ventricle (LV) is a marker for severe and extensive CAD (13–16), which has been shown to be of prognostic value (17,18). However, the prognostic value of TID in patients with an otherwise normal MPS has not been defined. Also of note, in many previous reports, patients with "normal" MPS could have minimal perfusion abnormalities or LV enlargement and were not distinguished from those with "perfectly" normal scans.

Our study was performed to evaluate the hypothesis that TID may have independent prognostic value in patients with normal MPS. To selectively evaluate the prognostic impact of TID, we studied patients with otherwise "perfectly" normal MPS and normal LV cavity size at rest; we also evaluated other independent predictors of increased cardiac risk in patients with "perfectly" normal MPS. Further, we assessed whether the findings regarding TID also applied to patients with the standard definition of normal MPS.

From the *Department of Imaging (Division of Nuclear Medicine) and Department of Medicine (Division of Cardiology), Cedars-Sinai Medical Center, Los Angeles, California; †Leiden University Medical Center, Leiden, the Netherlands; and ‡Keck School of Medicine, University of Southern California, Los Angeles, California. Supported, in part, by grants from Bristol-Myers Squibb Medical Imaging, Inc., Billerica, Massachusetts; and Fujisawa Healthcare, Inc., Deerfield, Illinois. Dr. Abidov is a Save A Heart Foundation/Max and Pauline Zimmer Family Foundation Research Fellow at Cedars-Sinai Medical Center, Los Angeles, California. Dr. James E. Udelson acted as Guest Editor for this manuscript.

Manuscript received April 8, 2003; revised manuscript received July 14, 2003, accepted July 17, 2003.

Abbreviations and Acronyms

CAD	= coronary artery disease
CD	= cardiac death
ECG	= electrocardiogram
HE	= hard cardiac events
LHR	= lung-heart ratio
LV	= left ventricle/ventricular
MI	= myocardial infarction
MPS	= myocardial perfusion single photon emission computed tomography
SE	= soft cardiac events
SPECT	= single photon emission computed tomography
SSS	= summed stress scores
TE	= total cardiac events
TID	= transient ischemic dilation of the left ventricle
^{201}Tl	= thallium-201
^{99m}Tc	= technetium-99m

METHODS

Study population. We identified 1,601 consecutive patients who underwent rest thallium-201 (^{201}Tl)/stress technetium-99m (^{99m}Tc)-sestamibi MPS, with no perfusion defects and no visual evidence of resting LV enlargement. With 41 lost to follow-up (2.6%), 1,560 patients comprised the primary study population (Population 1); 436 patients underwent vasodilator stress (387 adenosine, 49 dipyridamole); and 1,124 patients had exercise. Patients with previous MI or revascularization were considered to have known CAD.

We also evaluated a broader group of 2,037 patients in whom complete follow-up information was available (Population 2) (48.7% men; mean age 63.2 ± 12.8 years; 618 patients had vasodilator stress [556 adenosine, 62 dipyridamole] and 1,419 had exercise) defined as having normal MPS using our standard definition of normal scan, which includes 477 patients with minimal defects, considered too small to be called abnormal (1–7).

Imaging procedure. All patients underwent rest ^{201}Tl/stress ^{99m}Tc-sestamibi MPS as previously described (19). Whenever possible, beta-blockers and calcium channel antagonists were terminated 48 h before testing and nitrates at least 6 h before testing. Patients performed a symptom-limited exercise treadmill test or vasodilator (dipyridamole or adenosine) stress using standard protocols (20,21). Patients were instructed not to consume coffee or other products containing caffeine for 24 h before the test. During both types of stress, heart rate, blood pressure, and a 12-lead electrocardiogram (ECG) were recorded at baseline and every minute thereafter for at least 5 min. The ECG was monitored continuously (leads aVF, V_1, and V_5) for development of arrhythmia or ischemic ST-segment deviation (22). Blood pressure was measured and recorded at rest, at the end of each stress stage, and at peak stress.

Acquisition protocol. All patients underwent separate acquisition, dual isotope MPS (23). Myocardial perfusion SPECT was started 10 min after ^{201}Tl injection and 15 to 60 min after ^{99m}Tc-sestamibi injection. Myocardial perfusion SPECT employed circular or elliptical 180° acquisition for 64 projections at 20 to 25 s/projection for ^{201}Tl and at 15 to 25 s/projection for ^{99m}Tc-sestamibi. All images were subject to quality control measures. The projection data were reconstructed into tomographic transaxial images using filtered back projection and automatic reorientation (24). No attenuation or scatter correction was used.

Image interpretation. Semiquantitative visual interpretation was performed using the 20-segment model (1,19). Each segment was scored using a 5-point scoring system (0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of uptake, and 4 = absence of detectable tracer uptake). Summed stress scores (SSS) were obtained by summing the individual stress scores of the 20 segments. Only patients with MPS interpreted as normal with SSS = 0 and no visual evidence of resting LV enlargement were included in Population 1. Population 2 consisted of all patients with follow-up information who had a normal scan defined as SSS = 0 to 3 (13).

Measurement of TID. For calculation of TID, we used a commercially available automated program (QPS, Cedars-Sinai, Los Angeles, California), which estimates three-dimensional image volumes from gated or ungated SPECT studies (25). The software is completely automatic but does allow manual operator interaction if needed. 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 (16). For purposes of this study, the TID ratio calculated from the ungated SPECT studies was employed.

Patient follow-up. Patient follow-up (all >1 year) was performed as previously described (1) by individuals blinded to the patient's test results. All patients were followed up for HE (CD or nonfatal MI) (26,27); soft events (SE), defined by revascularization after an index MPS; and total events (TE), defined by the first HE or SE. Any revascularization after MPS was used rather than our usual late revascularization occurring >60 days (28,29) after MPS because, when normal, the results of the scan would not be expected to increase the rate of early coronary angiography. Cardiac death was defined as death due to any cardiovascular cause (26); MI was documented by a consistent history accompanied by elevation of cardiac enzymes and/or new Q waves on the ECG.

Statistical analysis. Comparisons between patient groups were performed using a *t* test for continuous variables or analysis of variance and chi-square for categorical variables. All continuous variables were described as a mean ± SD. A p value <0.05 was considered significant.

Due to few observed HE, we studied the prediction of TE using multivariable Cox proportional hazards analysis. Selection of variables for consideration for entry was based on univariable statistical significance and clinical judgment

Table 1. Distribution of the Study Population 1 by Quartiles of TID Ratio

Subgroup	Number of Patients	Mean ± SD of TID Ratio	Range of TID Ratio (Minimum-Maximum)
1st quartile	361	0.93 ± 0.06	0.80–0.99
2nd quartile	400	1.02 ± 0.02	1.00–1.07
3rd quartile	409	1.13 ± 0.04	1.08–1.20
4th quartile	390	1.35 ± 0.14*	1.21–1.79

*p = 0.001 across the groups.
TID = transient ischemic dilation.

(21). A significant increase in global chi-square of a model after addition of a variable indicated incremental prognostic value. Variables in the final model were tested for confounding, interactions, and linearity.

RESULTS

Follow-up events. In Population 1, during follow-up of 2.30 ± 0.67 years, there were 13 HE (6 CD and 7 nonfatal MI) and 36 SE; 42 patients (2.7%) had TE. Of the 36 SE, none occurred <60 days after SPECT. The annualized event rate was low: 0.2%/year for CD, 0.25%/year for MI, 0.4%/year for HE, and 1.2%/year for TE. Hard events and TE rates were higher with vasodilator than with exercise stress: (HE and TE rates 1.0% and 1.9%/year for vasodilator stress vs. 0.3% and 0.9%/year for exercise stress, respectively, $p < 0.01$ for both).

In Population 2, during follow-up of 2.26 ± 0.69 years, there were 19 HE (10 CD and 9 nonfatal MI) and 52 SE; 61 patients (3.0%) had TE. Of the 52 SE, 7 (13.5%) occurred <60 days after SPECT. The annualized event rate for Population 2 was as low as for Population 1: 0.2%/year for CD, 0.2%/year for MI, 0.4%/year for HE, and 1.3%/year for TE. Hard events and TE rates were higher in the Population 2 with vasodilator than with exercise stress: (HE and TE rates 0.9% and 2.0%/year for vasodilator stress vs. 0.2% and 1.0%/year for exercise stress, respectively, $p < 0.01$ for both). When only the 477 patients with SSS = 1 to 3 were considered, the annualized event rates were 0.6%/year for HE and 1.4%/year for TE. These rates were not different from those observed in the patients with SSS = 0 (Population 1).

Prediction of events in Population 1: (SSS = 0). Cardiac risk of patients with different values of TID ratio. Population 1 was separated into quartiles based on the TID ratio (Table 1). Patients in the highest quartile had a TID ratio that was similar in patients with the exercise and vasodilator stress (1.36 ± 0.16 vs. 1.35 ± 0.13, $p = 0.505$) and was well above the previously validated normal TID limit of 1.22 (16). The risks for both TE and HE were higher in the highest TID ratio quartile (Fig. 1); patients in the three lower quartiles all had the same low risk of future cardiac events. Accordingly, the patients in the three lower TID ratio quartiles were combined as a control group for comparison with the patients in the highest TID ratio quartile. Patients in the control group had a low risk of TE

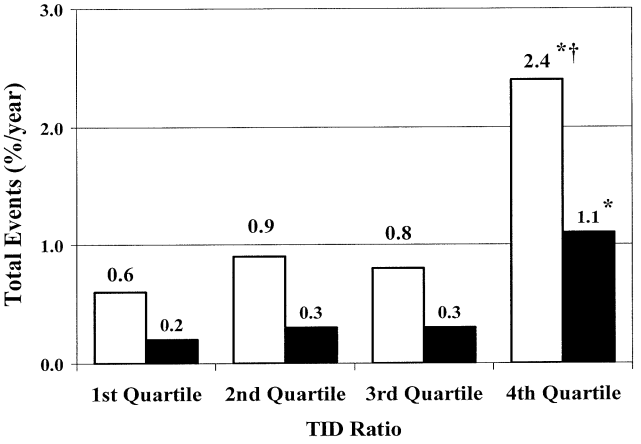

Figure 1. Annual rates of first future cardiac events (total events) and hard events in patients with normal myocardial perfusion single photon emission computed tomography distributed by quartiles of transient ischemic dilation (TID) ratio. *$p < 0.001$ across the groups; †$p = 0.006$ for highest quartile versus all others. **Open bars** = total events; **solid bars** = hard events.

(≤1%/year both in exercise and vasodilator stress subgroups); however, patients in the highest TID quartile had an intermediate risk of TE with exercise (1.8%/year), and high risk of TE with vasodilator stress (3.2%/year) (Fig. 2).

Clinical characteristics of patients in the highest TID quartile versus controls. Compared with the control group, patients in the highest TID quartile were older, included more women, were less able to perform exercise, and more often had diabetes (all $p < 0.01$) (Table 2).

Risk of TE by univariable analysis. By univariable analysis, the most significant predictors of TE in Population 1 were diabetes and the highest TID quartile (both $p < 0.001$) (Table 3). The highest TID quartile conferred a threefold higher TE rate compared with others (2.4% vs. 0.8%/year, $p = 0.001$). Other significant predictors of TE were age >75 years, prior percutaneous intervention, history of known CAD (prior MI/revascularization), vasodilator stress, and typical angina. Of note, the presence of an

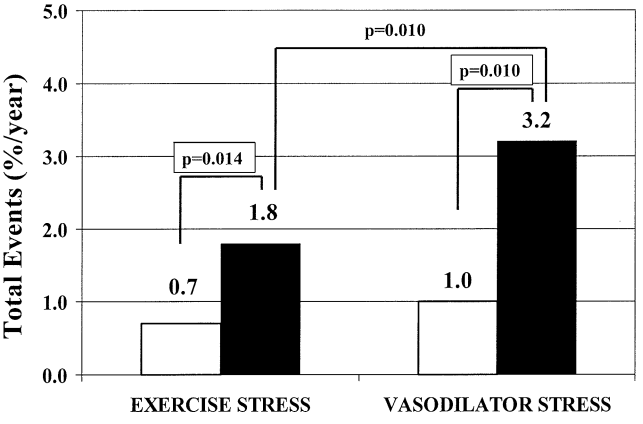

Figure 2. Annual total event rate as a function of stress type and presence of highest transient ischemic dilation (TID) quartile; controls are patients in three lower quartiles of TID. **Open bars** = controls; **solid bars** = highest quartile of TID.

Table 2. Clinical Characteristics of Patients in the Highest TID Ratio Quartile Versus Lower Quartiles

Variables	Highest TID Ratio Quartile (n = 390)	Lower Quartiles of TID Ratio (n = 1,170)	p Value
Age	66.1 ± 12.8	61.8 ± 12.8	<0.001
Male gender	168 (43.1%)	611 (52.2%)	0.002
Exercise stress	215 (55.1%)	909 (77.7%)	<0.001
Prior MI	34 (8.7%)	69 (5.9%)	0.052
Prior PCI/CABG	35 (9.0%)	99 (8.5%)	0.130
Known CAD	52 (13.3%)	130 (10.7%)	0.160
Diabetes	55 (14.1%)	104 (8.9%)	0.003
Hypertension	182 (46.7%)	514 (43.9%)	0.347
Typical angina	40 (10.3%)	113 (9.7%)	0.731
SOB	22 (5.6%)	49 (4.2%)	0.233
Ischemic ECG response	41 (10.5%)	161 (13.8%)	0.098

CABG = coronary artery bypass grafting; known CAD = history of prior myocardial infarction (MI) or revascularization; PCI = percutaneous coronary intervention; SOB = shortness of breath; TID = transient ischemic dilation of the left ventricle.

ischemic ECG response was not associated with an increased risk of TE by univariable analysis.

Prediction of TE by multivariable analysis. Using Cox multivariable proportional hazards analysis, we tested the significant univariable predictors of TE as well as history of CAD and ischemic ECG response (Table 4). Significant variables in the final multivariable model were age, diabetes, typical angina, and the highest quartile of TID (Table 4). The highest TID quartile was an independent and incremental predictor of TE-free survival (Fig. 3), leading to significant increase in global chi-square from 39.8 (model including the age, diabetes, and typical angina variables) to 49.2 (absolute gain in global chi-square = 9.4, p = 0.008). There was no evidence of confounding or interaction between the tested variables in this model.

Prediction of TE in Population 2: (SSS = 0 to 3). In Population 2, the highest TID quartile conferred a two-fold higher TE rate compared with others (2.2% vs. 1.0%/year, p = 0.002). The highest TID quartile was a significant univariable (odds ratio [OR] = 2.2, 95% confidence interval [CI] = 1.3 to 3.6) and multivariable (hazard ratio = 1.8, 95% CI = 1.1 to 3.1) predictor of TE in Population 2. The final Cox multivariable model for the prediction of TE in this population included not only diabetes, age, and typical angina, but also history of CAD.

Table 3. Results of Univariable Analysis for Prediction of TE

Variables	Odds Ratio	95% Confidence Interval	p Value
Age >75 yrs	2.75	1.44–5.25	0.001
Female gender	0.68	0.36–1.27	0.222
Prior MI	0.70	0.17–2.94	0.626
Prior PCI	2.88	1.10–7.56	0.025
Prior CABG	2.70	0.93–7.82	0.057
Known CAD	6.06	1.20–4.96	0.014
Hypertension	1.52	0.82–2.81	0.180
Hyperlipidemia	0.61	0.32–1.64	0.130
Diabetes	4.21	2.14–8.28	<0.001
Vasodilator stress	2.18	1.18–4.04	0.011
Typical angina	3.00	1.45–6.24	0.002
SOB	1.05	0.25–4.34	0.947
Ischemic ECG response	0.91	0.35–2.33	0.838
Highest quartile of TID	3.44	1.85–6.37	<0.001

TE = total events. Other abbreviations as in Table 2.

Angiographic correlations in Population 1. Sixty-five of the patients with entirely normal scans underwent follow-up coronary angiography, and the angiographic data were available for analysis in 53 (81.5%). Patients in the highest TID quartile more often had CAD (≥70% luminal stenosis) in at least one of the three major coronary arteries than patients in the control group (12/20 [60%] vs. 11/33 [33%], p = 0.058); only patients with TID had severe and extensive CAD as defined by >90% stenosis of the proximal LAD or of multiple vessels (16) (5/20 [25%] vs. 0/33 [0%], p = 0.003).

DISCUSSION

Our findings demonstrate that a stress MPS study with entirely normal perfusion and normal ventricular size does not always imply an excellent prognosis. In the current study, automatically measured TID yielded incremental prognostic value over clinical and historical variables in patients with otherwise normal MPS results. The patients with substantial TID (highest TID quartile) had a higher cardiac event rate compared with the other patients (2.4% vs. <1%/year in the lower three quartiles, p < 0.001). Significant variables in the final multivariable model for prediction of first future cardiac events in this population included age, diabetes, typical angina, and the highest quartile of TID. To the best of our knowledge, this is the first time that TID has been shown to be useful in risk stratification of patients with otherwise normal MPS results.

Comparison with previous studies. Patients with normal MPS have a very low risk of HE (usually <1%/year) (6,10,11,27); nonetheless, a small proportion of patients with normal MPS do develop future cardiac events. In a recent report, we found that age, gender, diabetes, type of stress, and a history of known CAD are multivariable predictors of cardiac events in this low-risk population (12). We also reported significant interactions between stress type and previous CAD (lower risk in patients without previous CAD undergoing exercise stress vs. all others) and between diabetes and gender (higher risk in diabetic females) (12), but we did not investigate TID in this previous report. Furthermore, most previous prognostic reports of patients with normal MPS have not distinguished those with minimal perfusion abnormalities or LV enlargement from those with "perfectly" normal scans. In this study we examined the prognostic value of TID and other variables in a large population of patients with no perfusion abnormality on dual isotope MPS (SSS = 0) and no resting LV enlargement as well as in the broader group of patients with normal MPS (SSS = 1 to 3). Previous work from our group has indicated that automatically measured dual isotope TID

Table 4. Final Cox Proportional Hazards Model for the Prediction of TE*

Variable in the Model	Chi-Square	Hazard Ratio (95% Confidence Interval)	p Value
Diabetes	13.9	3.51 (1.81–6.79)	<0.001
Typical angina	7.4	2.67 (1.31–5.44)	0.007
Age	7.2	1.04 (1.01–1.06)	0.007
Highest quartile of TID	7.1	2.34 (1.25–4.36)	0.008

*Global Chi-square of the model = 43.2; $p < 0.001$.
TE = total events; TID = transient ischemic dilation of the left ventricle.

using QPS software is sensitive and highly specific for detection of severe and extensive CAD (16). Peace et al. (28) found that TID in Tc-99m tetrofosmin MPS, measured by six different algorithms, is an indicator of severe CAD, and all existing algorithms provided a repeatable, quantitative measure of the TID. These measures have not been previously assessed for prognostic value in patients with normal MPS.

Which patients with normal MPS are at increased risk? We have previously shown that increased age, noncardiac comorbidities (in particular diabetes), prior CAD, and vasodilator stress are associated with a higher event rate in patients with normal MPS (12,21,29), suggesting that underlying clinical conditions influence their cardiac prognosis after a normal perfusion study (3,17).

A new finding in our study is the incremental prognostic value of an abnormal TID ratio in patients with normal perfusion in a multivariable model including all other significant markers. Clinical characteristics that were predictive in patients with entirely normal scans (SSS = 0, normal LV cavity at rest) included age, typical angina, and diabetes. Other clinical variables previously associated with an increased cardiac event risk (21) did not emerge in the final prognostic model; in patients with entirely normal MPS, prior MI and history of revascularization or the composite variable, history of known CAD, were not predictive of future cardiac events. These findings are likely to be related to characteristics of the present study population and to the smaller number of events in the current population than in our previous work (12).

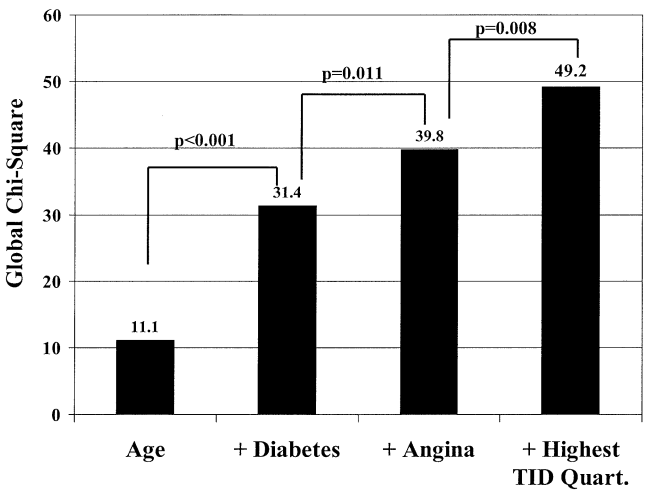

Figure 3. Incremental value of the presence of highest transient ischemic dilation (TID) quartile in prediction of total events in patients with normal myocardial perfusion single photon emission computed tomography.

In the broader population of patients with normal scans defined by our standard criteria (SSS = 0 to 3), follow-up TE and HE rates were as low as in patients in the main study population (SSS = 0); TID in patients with SSS = 0 to 3 also was found to be predictive of TE by both univariable and multivariable analysis. Of interest, the HE rate was as low in this group as in the group with the entirely normal scans. When the small group of patients with SSS = 1 to 3 was separately analyzed, there were no differences noted in HE and TE rates compared with the patients with SSS = 0.

Possible mechanisms of prognostic impact of the TID in patients with normal MPS. Transient ischemic dilation of the LV and increased lung-heart ratio (LHR) are both associated with severe CAD (13–16,30–32). Increased LHR with ^{201}Tl has been shown to be valuable in evaluation of prognosis in patients with myocardial perfusion abnormalities (33,34), but does not appear to risk-stratify patients with normal MPS (33,35). A number of clinical studies have demonstrated in multiple settings that the presence of TID on MPS predicts left main or severe multivessel CAD (13,14,36–40) or adverse cardiac outcome (18,41). The underlying mechanisms of TID are likely to be varied, with some pathologic and others physiologic. Probably the most common pathologic mechanism is "apparent" (as opposed to "true") TID caused by nonvisualization of the extensive amount of the subendocardial myocardium after stress in the presence of severe stress-induced ischemia/hypoperfusion (15,37,38,42). The measurement of TID employed in this manuscript relies on the automatic definition of endocardial boundaries of the LV. The presence of stress-induced subendocardial ischemia can result in an apparent thinning of the myocardium and a consequent overestimation of true LV cavity size. Because the subendocardium in this setting would generally have resting perfusion that is either normal or not as hypoperfused as during stress, the measured resting LV volume would appear smaller than the post-stress volume, even if the true volumes were the same.

Another pathologic mechanism is true TID in which the LV dilates during stress and remains dilated through the post-stress MPS imaging (43,44). This mechanism would imply the presence of stress-induced stunning of enough of

the LV to cause overall enlargement. This stress-induced stunning is a well-described phenomenon, associated with critical coronary stenosis (45). Evidence of the presence of true transient dilation in many of the patients with TID was provided in the initial description of the abnormal TID ratio in which the TID defined by the epicardial edges of the LV on planar ^{201}Tl images was predictive of severe and extensive CAD (13). The presence of this mechanism was further supported by the findings in the preliminary report of the automatically measured SPECT TID ratio, not included in the final manuscript (16). When this ratio was derived from the epicardial edges of the LV, it was predictive of severe and extensive CAD, although less so than that derived from the endocardial edges (16).

Regarding the finding of an abnormal TID ratio in patients with otherwise normal MPS scans, either of these mechanisms would be expected to result in increased risk of events. In the case of subendocardial ischemia, the ischemia would most likely be diffuse and extensive in order to explain the absence of an apparent relative perfusion defect. Similarly, true transient dilation persisting through the post-stress scanning time would be expected to be associated with severe and diffuse stress-induced ischemia. The current findings demonstrate that abnormal automatically measured TID ratio has prognostic value in patients with a normal perfusion and should, thus, be considered in the prognostic assessment of these patients. Both of these mechanisms would imply that an increased TID ratio could be related to diffuse, "balanced ischemia" due to severe CAD (46).

Thus, our results showing increased event rates in patients with normal MPS and TID may be explained by severe underlying CAD in these patients, missed by perfusion defect analysis alone. The limited data from coronary angiography in our Population 1 support this postulation. Obstructive CAD was more common in the patients with TID than in the controls ($p = 0.058$), and severe and extensive CAD was found only in patients with TID.

Recent published data (47) demonstrated that, in patients with classical syndrome X (with normal MPS in the majority), magnetic resonance spectroscopy revealed subendocardial hypoperfusion following intravenous administration of adenosine, implying another possible pathologic mechanism for apparent TID without extensive coronary atherosclerosis. However, it is likely that in many patients TID is simply physiologic, occurring as a variant of normal for reasons that are not yet understood.

Study limitations. The present study used different radionuclides to produce the rest and stress images adding complexity to the comparison of stress and rest volumes; as previously shown, however, the automatic algorithm used in our study for measuring the TID ratio has been shown to be effective in identifying severe and extensive CAD in dual-isotope studies (16). If applied to single radionuclide studies, the cut-off for an abnormal TID ratio might be different, but the mechanisms likely to be operative in this study should still apply. Although it has been shown that automated TID calculations using different software methods are similar (28), the data presented in this paper apply to the TID ratio derived using QPS software; further studies would be required to determine if these results apply to other software programs. Due to the small number of HE in the study population, the multivariable prognostic assessment analysis was limited to the prediction of TE. The current results are based on a population referred for nuclear testing and, therefore, may not be applicable to a broader population; however, the patients in this study are typical of those referred to a university-affiliated community hospital in a major urban area, and the results of this study should be applicable to this setting. This study is retrospective in nature. Although all data were collected and entered prospectively, further confirmation of our findings in other populations is needed. Finally, the study is based on data of a single nuclear cardiology center with unique technical characteristics, which may not be applicable in other nuclear laboratories.

Clinical implications. In patients with elevated TID ratio and otherwise normal MPS, the total event rates are increased, but only to intermediate levels. Given this, we do not believe that patients need to be considered as candidates for coronary angiography on the basis of an increased TID alone. However, when integrated with all other available information (e.g., typical angina, advanced age, and diabetes), the finding of increased TID may be useful in selecting of patients at sufficiently increased risk that coronary angiography or further noninvasive testing (e.g., noninvasive coronary angiography) would be appropriate.

Conclusions. An entirely normal stress MPS study does not always imply an excellent prognosis. In patients with otherwise normal MPS, TID is an independent and incremental prognostic marker of TE even after significant clinical variables—age, typical angina, and diabetes—are accounted for. When TID is present, caution in making low-risk prognostic statements may be warranted, especially in patients with typical angina, the elderly, and diabetics. Our findings also appear to apply to the broader population of "normal" MPS, which included patients with minimal perfusion defects.

Reprint requests and correspondence: Dr. Daniel S. Berman, Department of Imaging, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Taper Building, A1258, Los Angeles, California 90048. E-mail: bermand@cshs.org.

REFERENCES

1. Berman DS, Hachamovitch R, Kiat H, et al. Incremental value of prognostic testing in patients with known or suspected ischemic heart disease: a basis for optimal utilization of exercise technetium-99m sestamibi myocardial perfusion single-photon emission computed tomography. J Am Coll Cardiol 1995;26:639–47.
2. Hachamovitch R, Berman DS, Kiat H, et al. Effective risk stratification using exercise myocardial perfusion SPECT in women: gender-related differences in prognostic nuclear testing. J Am Coll Cardiol 1996;28:34–44.

3. Hachamovitch R, Berman DS, Kiat H, et al. Incremental prognostic value of adenosine stress myocardial perfusion single-photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. Am J Cardiol 1997;80:426–33.
4. Hachamovitch R, Shaw LJ, Berman DS. The ongoing evolution of risk stratification using myocardial perfusion imaging in patients with known or suspected coronary artery disease. ACC Curr J Rev 1999; 8:66–71.
5. Hachamovitch R. Prognostic characterization of patients with mild coronary artery disease with myocardial perfusion single photon emission computed tomography: validation of an outcomes-based strategy (editorial comment). J Nucl Cardiol 1998;5:90–5.
6. Hachamovitch R, Berman DS, Shaw LJ, et al. Incremental prognostic value of myocardial perfusion single photon emission computed tomography for the prediction of cardiac death: differential stratification for risk of cardiac death and myocardial infarction. Circulation 1998;97:535–43.
7. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. J Am Coll Cardiol 1998;32:57–62.
8. Ritchie JL, Bateman TM, Bonow RO, et al. Guidelines for clinical use of cardiac radionuclide imaging: a report of the American College of Cardiology/American Heart Association Task Force on assessment of diagnostic and therapeutic cardiovascular procedures (Committee on Radionuclide Imaging)—developed in collaboration with the American Society of Nuclear Cardiology. J Nucl Cardiol 1995;2:172–92.
9. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Chronic Stable Angina). J Am Coll Cardiol 1999;33:2092–197.
10. Soman P, Parsons A, Lahiri N, Lahiri A. The prognostic value of a normal Tc-99m sestamibi SPECT study in suspected coronary artery disease. J Nucl Cardiol 1999;6:252–6.
11. Galassi AR, Azzarelli S, Tomaselli A, et al. Incremental prognostic value of technetium-99m-tetrofosmin exercise myocardial perfusion imaging for predicting outcomes in patients with suspected or known coronary artery disease. Am J Cardiol 2001;88:101–6.
12. Hachamovitch R, Hayes SW, Friedman JD, et al. Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans. What is the warranty period of a normal scan? J Am Coll Cardiol 2003;41:1329–40.
13. Weiss AT, Berman DS, Lew AS, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: a marker of severe and extensive coronary artery disease. J Am Coll Cardiol 1987;9:752–9.
14. Chouraqui P, Rodrigues EA, Berman DS, Maddahi J. Significance of dipyridamole-induced transient dilation of the left ventricle during thallium-201 scintigraphy in suspected coronary artery disease. Am J Cardiol 1990;66:689–94.
15. Iskandrian AS, Heo J, Nguyen T, Lyons E, Paugh E. Left ventricular dilatation and pulmonary thallium uptake after single-photon emission computer tomography using thallium-201 during adenosine-induced coronary hyperemia. Am J Cardiol 1990;66:807–11.
16. Mazzanti M, Germano G, Kiat H, et al. Identification of severe and extensive coronary artery disease by automatic measurement of transient ischemic dilation of the left ventricle in dual-isotope myocardial perfusion SPECT. J Am Coll Cardiol 1996;27:1612–20.
17. Lette J, Bertrand C, Gossard D, et al. Long-term risk stratification with dipyridamole imaging. Am Heart J 1995;129:880–6.
18. McClellan JR, Travin MI, Herman SD, et al. Prognostic importance of scintigraphic left ventricular cavity dilation during intravenous dipyridamole technetium-99m sestamibi myocardial tomographic imaging in predicting coronary events. Am J Cardiol 1997;79:600–5.
19. Berman DS, Kiat H, Friedman JD, et al. Separate acquisition rest thallium-201/stress technetium-99m sestamibi dual-isotope myocardial perfusion single-photon emission computed tomography: a clinical validation study. J Am Coll Cardiol 1993;22:1455–64.
20. Matzer L, Kiat H, Wang FP, et al. Pharmacologic stress dual-isotope myocardial perfusion single-photon emission computed tomography. Am Heart J 1994;128:1067–76.
21. Berman DS, Kang X, Hayes SW, et al. Adenosine myocardial perfusion SPECT in women compared to men: impact of diabetes mellitus on incremental prognostic value and effect on patient management. J Am Coll Cardiol 2003;41:1125–33.
22. Amanullah AM, Berman DS, Kiat H, Friedman JD. Usefulness of hemodynamic changes during adenosine infusion in predicting the diagnostic accuracy of adenosine technetium-99m sestamibi single-photon emission computed tomography (SPECT). Am J Cardiol 1997;79:1319–22.
23. Van Train KF, Areeda J, Garcia EV, et al. Quantitative same-day rest-stress technetium-99m-sestamibi SPECT: definition and validation of stress normal limits and criteria for abnormality. J Nucl Med 1993;34:1494–502.
24. Germano G, Kavanagh PB, Su HT, et al. Automatic reorientation of three-dimensional, transaxial myocardial perfusion SPECT images (see comments). J Nucl Med 1995;36:1107–14.
25. Germano G, Kiat H, Kavanagh PB, et al. Automatic quantification of ejection fraction from gated myocardial perfusion SPECT. J Nucl Med 1995;36:2138–47.
26. Sharir T, Germano G, Kang X, et al. Prediction of myocardial infarction versus cardiac death by gated myocardial perfusion SPECT: risk stratification by the amount of stress-induced ischemia and the poststress ejection fraction. J Nucl Med 2001;42:831–7.
27. Brown KA, Altland E, Rowen M. Prognostic value of normal technetium-99m-sestamibi cardiac imaging. J Nucl Med 1994;35: 554–7.
28. Peace RA, McKiddie FI, Staff RT, Gemmell HG. Comparison of methods for quantification of transient ischaemic dilation in myocardial perfusion SPECT. Nucl Med Commun 2000;21:971–6.
29. Heller GV, Herman SD, Travin MI, Baron JI, Santos-Ocampo C, McClellan JR. Independent prognostic value of intravenous dipyridamole with technetium-99m sestamibi tomographic imaging in predicting cardiac events and cardiac-related hospital admissions: PG-1202-8. J Am Coll Cardiol 1995;26:1202–8.
30. Bingham JB, McKusick KA, Strauss HW, Boucher CA, Pohost GM. Influence of coronary artery disease on pulmonary uptake of thallium-201. Am J Cardiol 1980;46:821–6.
31. Boucher CA, Zir LM, Beller GA, et al. Increased lung uptake of thallium-201 during exercise myocardial imaging: clinical, hemodynamic and angiographic implications in patients with coronary artery disease. Am J Cardiol 1980;46:189–96.
32. Kushner FG, Okada RD, Kirshenbaum HD, Boucher CA, Strauss HW, Pohost GM. Lung thallium-201 uptake after stress testing in patients with coronary artery disease. Circulation 1981;63:341–7.
33. Kaminek M, Myslivecek M, Skvarilova M, et al. Increased prognostic value of combined myocardial perfusion SPECT imaging and the quantification of lung Tl-201 uptake. Clin Nucl Med 2002;27:255–60.
34. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med 1987;317: 1486–9.
35. Zafrir N, Dahlberg ST, Villegas BJ, Leppo JA. Prognostic utility of increased pulmonary thallium uptake in patients without ischemia. J Nucl Cardiol 1996;3:301–7.
36. Takeishi Y, Chiba J, Abe S, Komatani A, Takahashi K, Tomoike H. Noninvasive identification of left main and three-vessel coronary artery disease by thallium-201 single photon emission computed tomography during adenosine infusion. Ann Nucl Med 1994;8:1–7.
37. Marcassa C, Galli M, Baroffio C, Campini R, Giannuzzi P. Transient left ventricular dilation at quantitative stress-rest sestamibi tomography: clinical, electrocardiographic, and angiographic correlates. J Nucl Cardiol 1999;6:397–405.
38. Hansen CL, Sangrigoli R, Nkadi E, Kramer M. Comparison of pulmonary uptake with transient cavity dilation after exercise thallium-201 perfusion imaging. J Am Coll Cardiol 1999;33:1323–7.
39. Romanens M, Gradel C, Saner H, Pfisterer M. Comparison of 99mTc-sestamibi lung/heart ratio, transient ischaemic dilation and perfusion defect size for the identification of severe and extensive coronary artery disease. Eur J Nucl Med 2001;28:907–10.
40. Kinoshita N, Sugihara H, Adachi Y, et al. Assessment of transient left ventricular dilatation on rest and exercise on Tc-99m tetrofosmin myocardial SPECT. Clin Nucl Med 2002;27:34–9.

41. Lette J, Lapointe J, Waters D, Cerino M, Picard M, Gagnon A. Transient left ventricular cavitary dilation during dipyridamole-thallium imaging as an indicator of severe coronary artery disease. Am J Cardiol 1990;66:1163–70.
42. Takeishi Y, Tono-oka I, Ikeda K, Komatani A, Tsuiki K, Yasui S. Dilatation of the left ventricular cavity on dipyridamole thallium-201 imaging: a new marker of triple-vessel disease. Am Heart J 1991;121: 466–75.
43. Van Tosh A, Hecht S, Berger M, Roberti R, Luna E, Horowitz SF. Exercise echocardiographic correlates of transient dilatation of the left ventricular cavity on exercise thallium-201 SPECT imaging. Chest 1994;106:1725–9.
44. Bestetti A, Di Leo C, Alessi A, Triulzi A, Tagliabue L, Tarolo GL. Post-stress end-systolic left ventricular dilation: a marker of endocardial post-ischemic stunning. Nucl Med Commun 2001;22:685–93.
45. Johnson LL, Verdesca SA, Aude WY, et al. Postischemic stunning can affect left ventricular ejection fraction and regional wall motion on post-stress gated sestamibi tomograms. J Am Coll Cardiol 1997;30: 1641–8.
46. McLaughlin MG, Danias PG. Transient ischemic dilation: a powerful diagnostic and prognostic finding of stress myocardial perfusion imaging. J Nucl Cardiol 2002;9:663–7.
47. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002;346:1948–53.