
The Role of Left Ventricular Hypertrophy and Diabetes in the Presence of Transient Ischemic Dilation of the Left Ventricle on Myocardial Perfusion SPECT Images

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Transient ischemic dilation of the left ventricle found on SPECT myocardial perfusion imaging (MPI) is an accepted marker of severe and extensive coronary artery disease (CAD) and poor prognosis. The influence of other clinical variables on the incidence of transient ischemic dilation is less certain. The aim of this study was to investigate clinical factors that may influence the incidence of transient ischemic dilation. In particular, we looked at factors that may independently affect subendocardial perfusion, such as left ventricular hypertrophy (LVH) and diabetes. **Methods:** MPI studies of 103 consecutive patients who had undergone recent coronary angiography (≤ 6 mo) and transthoracic echocardiography within a year of stress electrocardiography-gated MPI were retrospectively analyzed. Transient ischemic dilation was assessed quantitatively using a software program. A ratio cutoff of ≥ 1.22 was considered to represent transient ischemic dilation. Summed stress score and summed difference score (ischemia score) were determined using the standard 17-segment 5-point scoring system to quantify myocardial ischemia. LVH was defined as a left ventricular wall thickness of >11 mm on M-mode echocardiography. Severe CAD was defined as severe stenosis ($\geq 90\%$) of either the left anterior descending artery or both the right coronary and lateral circumflex arteries. **Results:** Nineteen (18%) of the 103 patients had transient ischemic dilation, 19 (18%) had LVH, and 23 (22%) were diabetic. A high percentage had severe CAD (46/103 [45%]), whereas 57 of 103 (55%) had less severe CAD (30/103 [29%]) or nonsignificant CAD (26/103 [25%]). Severe CAD ($P < 0.001$), diabetes ($P < 0.0001$), LVH ($P < 0.003$), and the ischemia score ($P < 0.023$) were independent predictors of transient ischemic dilation by multivariate logistic regression. In patients with severe CAD, the effect of LVH on the incidence of transient ischemic dilation was additive, increasing the incidence from 21% (8/38) without LVH to 75% (6/8) with LVH ($P < 0.006$). Likewise, with severe CAD, the incidence of transient ischemic dilation rose from 21% (7/33) in patients without dia-

betes to 54% (7/13) in those with diabetes ($P < 0.04$). **Conclusion:** The presence of transient ischemic dilation on myocardial perfusion SPECT is associated with the presence of severe CAD, but this association is modified by the presence of LVH and diabetes.

Key Words: myocardial perfusion imaging; transient ischemic dilation; left ventricular hypertrophy; coronary artery disease; diabetes

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Myo-cardial perfusion imaging (MPI) is a powerful diagnostic and prognostic tool for evaluating coronary artery disease (CAD). Prognostic indicators on MPI include the severity of both fixed and reversible perfusion defects (myocardial infarction and ischemia) (1), reduced left ventricular function after stress (2,3), and dilation of the left ventricle after stress (4–6).

The presence of transient ischemic dilation of the left ventricle on MPI is considered to be a marker of severe and extensive CAD and has been demonstrated after both pharmacologic and exercise stress (4,6–15). Until recently (6), the significance of finding transient ischemic dilation in the absence of apparent focal ischemia on the myocardial perfusion image had not been addressed. It is unclear whether this finding signifies the presence of balanced ischemia and triple-vessel disease, as previously assumed, or whether other physiologic factors are at play in the appearance of transient ischemic dilation on myocardial perfusion SPECT. The aim of this study was to investigate clinical factors that may influence the incidence of transient ischemic dilation, particularly those factors that may independently affect subendocardial perfusion, such as left ventricular hypertrophy (LVH) and diabetes.

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MATERIALS AND METHODS

Study Population

Medical records and investigations of consecutive patients who had undergone routine single-day ^{99m}Tc -sestamibi myocardial SPECT between January 2000 and December 2001 were reviewed. Patients were included in the study if they had undergone coronary angiography within 6 mo of their MPI, with no intervening cardiac event (myocardial infarction or revascularization procedure), and had undergone transthoracic echocardiography within 1 y. A total of 103 patients fulfilled the entry criteria and were included in the study. A diagnosis of diabetes was determined on the basis of a patient history of diabetes and a current requirement for oral diabetic medication or insulin.

Stress Protocol

Exercise stress was applied to 24 patients using a Bruce protocol treadmill test. Endpoints for exercise stress included achievement of 85% of target heart rate, >2-mm ST segment depression on the exercise electrocardiogram, or typical ischemic chest pain. A further 48 patients underwent a combined protocol, comprising a 4-min adenosine infusion with low-grade supplemental treadmill stress. The remaining 31 patients received a 4-min adenosine infusion without supplemental exercise.

All patients underwent a rest–stress MPI protocol, with 300 MBq of ^{99m}Tc -sestamibi injected for the rest image and between 1,200 and 1,400 MBq (dependent on patient weight) for the stress image.

SPECT Protocol

Images were obtained over a 180° orbit from right anterior oblique 45° to left posterior oblique 45° using a Siemens triple-head γ -camera equipped with high-resolution collimators. For image acquisition, a 20% acceptance window around the 140-keV photopeak was used. A 64 × 64 matrix was used for all studies. All raw data were reanalyzed for the study. The projection datasets were prefiltered using a Butterworth filter and reconstructed using filtered backprojection. The poststress images were gated for assessment of poststress left ventricular ejection fraction and wall motion. For all patients, standard 8-bin gating was applied using Siemens software. The raw data were reconstructed for all studies by a technologist experienced in nuclear cardiology.

Scan Interpretation

A transient ischemic dilation ratio derived from an automated software program, Emory Cardiac Toolbox (Syntermed, Inc.), was used for the assessment of transient ischemic dilation, with the previously validated cutoff of ≥ 1.22 chosen to represent transient ischemic dilation. Images were also interpreted visually and by consensus for the presence or absence of transient ischemic dilation, by 2 experienced observers who were unaware of the clinical and angiographic findings. The rest and poststress images were semiquantitatively interpreted for the presence, extent, severity, and reversibility of perfusion defects by 2 experienced physicians who were unaware of the clinical and angiographic findings. A 17-segment model of the left ventricle was used to score perfusion defect severity according to a 5-point system (0 = normal perfusion, 1 = equivocal or mildly reduced perfusion, 2 = moderately reduced perfusion, 3 = severely reduced perfusion, and 4 = absence of perfusion) (16). On the basis of this scoring system, a summed stress score and a summed difference score (ischemia score) were determined for each patient.

Echocardiography

Transthoracic echocardiography was performed on all patients (Vingmed Vivid 5; GE Healthcare). LVH was defined as a posterior or septal wall thickness of >11 mm as measured on M-mode echocardiography in the parasternal long-axis view, as previously described (17).

Angiographic Analysis

The coronary angiographic findings were retrospectively analyzed visually. CAD was considered absent if no major coronary arteries showed a $\geq 50\%$ reduction in lumen diameter. Severe CAD was defined as a $\geq 90\%$ stenosis of either the left anterior descending coronary artery or 2 or more major coronary vessels, a definition well validated in the assessment of transient ischemic dilation (6,14). For patients who previously underwent coronary artery bypass surgery, both the site and the severity of disease in native vessels and bypass grafts were documented. For each grafted vascular territory, stenosis of the bypass graft was used to define disease severity unless the graft was occluded, in which case the percentage stenosis of the native vessel was used.

Statistical Analysis

Continuous variables are reported as mean \pm SD. Categorical variables were compared using the χ^2 test. Multivariate stepwise logistic binary regression analysis was performed using variables that were significant by univariate analysis. All statistical analyses were performed using SPSS 11.0 software (SPSS Inc.). A *P* value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The characteristics of the patients are described in Table 1. The patients had undergone coronary angiography within a mean of 2.6 ± 2.4 mo of their MPI study. Forty-five percent (46/103) of patients had severe CAD, whereas 55% (57/103) had either less severe CAD (30/103) or nonhemodynamically significant CAD (26/103). Using a cutoff of ≥ 1.22 for the quantitative transient ischemic dilation ratio, 19 (18%) of the 103 patients had transient ischemic dilation. Nineteen patients (18%) had LVH identified on echocardiography (mean wall thickness, 13.5 ± 2.5 mm). Diabetes, diagnosed on the basis of a history of oral diabetic medication or insulin requirement, was present in 23 patients (22%).

Transient Ischemic Dilation

Severe CAD, LVH, severity of ischemia, the female sex, and diabetes all demonstrated a statistically significant association with the presence of transient ischemic dilation on χ^2 analysis (Table 1). Diabetes, LVH, severe CAD, and the ischemia score were all independent predictors of transient ischemic dilation by multivariate logistic regression (Table 2).

Severe CAD

Both the extent of ischemia and the presence of severe and extensive CAD on angiography were independent predictors of transient ischemic dilation (Table 2). As in previous studies (5,8,10,12,14), transient ischemic dilation was highly predictive of severe CAD on angiographic criteria, with an overall specificity of 93% (53/57) and a sensitivity

TABLE 1
Patient Characteristics

Variable	Overall	Transient ischemic dilation	No transient ischemic dilation	P
Age (mean ± SD)	68 ± 12	72 ± 8	68 ± 12	NS
Sex				<0.001*
Female	29/103 (28%)	10/19 (52%)	19/84 (23%)	
Male	74/103 (72%)	9/19 (47%)	65/84 (77%)	
Stress protocol				NS†
Exercise	24/103 (23%)	4/19 (21%)	20/84 (23%)	
Adenosine/exercise	31/103 (30%)	4/19 (21%)	27/84 (32%)	
Adenosine	48/103 (46%)	11/19 (57%)	37/84 (44%)	
CAD				<0.0001‡
Not severe	57/103 (55%)	4/19 (21%)	53/84 (63%)	
Severe	46/103 (45%)	15/19 (79%)	31/84 (36%)	
LVH	19/103 (18%)	8/19 (42%)	11/84 (13%)	<0.0001
Ischemia score (mean ± SD)	5.0 ± 5.9	8 ± 7.0	3 ± 3.7	<0.0001
Summed stress score (mean ± SD)	16 ± 13	24 ± 16	12 ± 10	<0.0001
Diabetes	23/103 (22%)	11/19 (58%)	12/84 (14%)	<0.0001
Coronary artery surgery	23/103 (22%)	4/19 (21%)	19/84 (22%)	NS

*Difference in incidence of transient ischemic dilation between men and women.

†Difference in incidence of transient ischemic dilation between different stress protocols.

‡Difference in incidence of transient ischemic dilation between severe and nonsevere CAD.

Other P values are for differences between transient ischemic dilation and no transient ischemic dilation.

NS = not statistically significant.

of 30% (14/46). However, in the presence of either LVH or diabetes, the specificity of transient ischemic dilation for severe CAD fell and the sensitivity rose (Table 3).

LVH

The majority (14/19 [74%]) of patients with LVH had a history of hypertension, 2 (11%) of 19 with LVH had diabetes, and 3 (16%) of 19 with LVH had neither a history of diabetes nor hypertension. No patients in the study had significant valvular disease or hypertrophic obstructive cardiomyopathy on echocardiography. LVH was an independent predictor of transient ischemic dilation on multivariate logistic regression (Table 2). A strong additive relationship was found between the presence of LVH and severe CAD and between the presence of LVH and the incidence of transient ischemic dilation (Fig. 1). In patients with severe CAD, the incidence of transient ischemic dilation increased from 21% (8/38) without LVH to 75% (6/8) with LVH ($P < 0.01$) (Fig. 1). Additionally, the specificity of transient ischemic dilation for the diagnosis of severe CAD decreased

from 95% in patients without LVH to 80% in patients with LVH (Table 3).

Diabetes

Diabetes was the strongest independent predictor of transient ischemic dilation on multivariate logistic regression ($P < 0.0001$) (Table 2). As with LVH, an incremental relationship was observed between diabetes, severe CAD, and the incidence of transient ischemic dilation (Fig. 2). In the presence of severe CAD, the incidence of transient ischemic dilation increased from 21% (7/33) without diabetes to 54% (7/13) with diabetes ($P < 0.04$) (Fig. 2). In the absence of severe CAD, the incidence of transient ischemic dilation rose from 2% (1/47) without diabetes to 30% (3/10) with diabetes ($P < 0.015$) (Fig. 2). Accordingly, the specificity of transient ischemic dilation for severe CAD fell from 98% in patients without diabetes to 70% in patients with diabetes (Table 3). Of the patients with both diabetes and LVH, all those with severe CAD (4/4 [100%]) had

TABLE 2
Multivariate Binary Logistic Regression Analysis
for Prediction of Transient Ischemic Dilation

Variable	F value	Mean square	P
Diabetes	18	8.0	0.0001
Severe CAD	12	8.0	0.001
LVH	9.2	6.2	0.003
Ischemia score	5.3	1.0	0.023

TABLE 3
Changes in Sensitivity and Specificity of Transient
Ischemic Dilation for Severe and Extensive CAD
With or Without LVH or Diabetes

Variable	Sensitivity	Specificity
Overall	30% (14/46)	93% (54/57)
LVH	75% (6/8)	80% (9/11)
No LVH	21% (8/38)	95% (44/46)
Diabetic	61% (8/13)	70% (7/10)
Nondiabetic	21% (7/33)	98% (46/47)

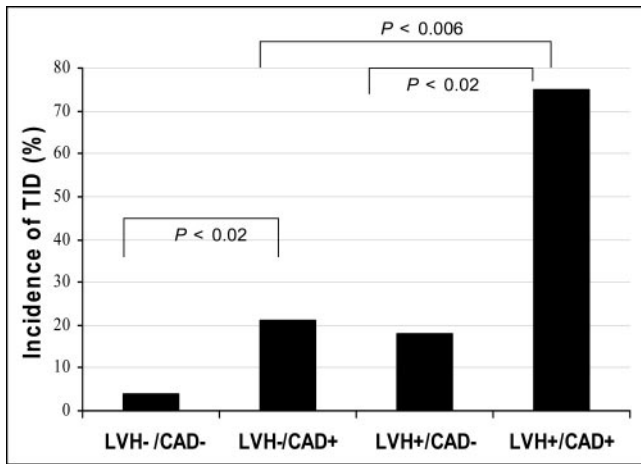


FIGURE 1. Effect of interaction between LVH and severe CAD on incidence of transient ischemic dilation. Incidence of transient ischemic dilation was higher in patients with both LVH and severe CAD than in patients with severe CAD alone ($P < 0.006$). Statistically significant difference in incidence of transient ischemic dilation was found between patients with and patients without severe CAD in absence and presence of LVH ($P = 0.02$). TID = transient ischemic dilation.

transient ischemic dilation, whereas those without severe CAD had a 50% (2/4) incidence of transient ischemic dilation.

Sex

Female patients demonstrated an increased incidence of transient ischemic dilation relative to male patients (10/29 [34%] vs. 9/74 [12%] $P < 0.01$). Further analysis revealed an increased prevalence of both diabetes and LVH among female patients relative to male patients (9/29 [31%] women and 14/74 [19%] men were diabetic; 7/29 [24%] women and 12/74 [16%] men had LVH). Consequently, multivariate analysis, accounting for the effect of LVH and diabetes, did not find the female sex to be an independent predictor of transient ischemic dilation.

Coronary Artery Bypass Grafting

A high proportion of the group (23/103) had undergone prior bypass surgery. The association between LVH, diabetes, ischemia, and transient ischemic dilation was unaffected when these patients were excluded from the analysis.

Visual Assessment of Transient Ischemic Dilation

The visual consensus method of determining the presence or absence of transient ischemic dilation resulted in classification of 27 (26%) of 103 patients as having transient ischemic dilation. Severity of ischemia, LVH, severity of CAD, and diabetes all remained independent predictors of transient ischemic dilation by multivariate binary logistic regression using this method. However, multivariate logistic regression showed that the strongest predictor of transient ischemic dilation was the burden of ischemia, not diabetes, on myocardial SPECT. Transient ischemic dilation remained highly predictive of severe CAD on angiographic

criteria, with an overall specificity of 81% (46/57) and a sensitivity of 39% (18/46).

DISCUSSION

Transient ischemic dilation is identified by an apparent increase in left ventricular cavity size on immediate post-stress myocardial perfusion images, compared with the size on resting myocardial perfusion images. This phenomenon was first described by Stolzenberg et al. in 1980 on planar ^{201}Tl images in a small group of patients (18). Subsequently, considerable literature has accumulated on the subject, covering exercise and pharmacologic stress SPECT and $^{99\text{m}}\text{Tc}$ -sestamibi MPI. Regardless of the agent used in MPI or the type of stress, transient ischemic dilation of the left ventricle on myocardial SPECT has become an accepted marker of severe and extensive CAD and of poor prognosis (4,6,8,10,12,14,15,19). This study confirmed that transient ischemic dilation is an important finding that can identify severe and extensive CAD and correlates well with the extent of ischemia demonstrated on myocardial SPECT. However, we found that both LVH and diabetes increase the incidence of transient ischemic dilation independently of the presence of angiographically severe CAD. This finding raises important questions about the pathophysiology of transient ischemic dilation seen on myocardial SPECT and the predictive value of transient ischemic dilation for severe CAD in the presence of either LVH or diabetes.

McClellan et al. (4) provided data indicating that transient ischemic dilation has an important prognostic role in patients undergoing dipyridamole stress testing with $^{99\text{m}}\text{Tc}$ -sestamibi SPECT. They followed 512 consecutive patients for 13 ± 7 mo. In the 14% with transient ischemic dilation, they found a cardiac event rate of 11%, compared with 2%

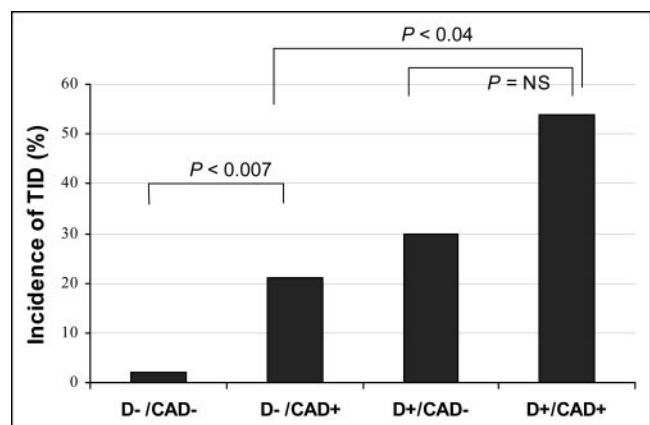


FIGURE 2. Effect of interaction between diabetes and severe CAD on incidence of transient ischemic dilation. In patients with severe CAD, incidence of transient ischemic dilation was significantly higher in subgroup with diabetes ($P < 0.04$). Statistically significant difference in incidence of transient ischemic dilation was found between severe CAD and less severe CAD in absence ($P < 0.007$), but not presence, of diabetes ($P = \text{NS}$). D = diabetes; TID = transient ischemic dilation.

in a group without transient ischemic dilation or fixed left ventricular dilatation. In contrast, a recent large study by Abidov et al. (6), assessing the prognosis of patients with transient ischemic dilation and normal perfusion on myocardial perfusion SPECT, found that those with transient ischemic dilation demonstrated a 2.4%-per-year cardiac event rate, compared with an event rate of less than 1% per year for patients with no transient ischemic dilation. This rate is far lower than the 11%-per-year cardiac event rate reported for patients with transient ischemic dilation by McClellan et al. The difference almost certainly reflects the higher prevalence of ischemia in the population of the McClellan study. In the past, the commonly accepted explanation for transient ischemic dilation in the presence of "normal perfusion" was thought to be "balanced ischemia" and multivessel CAD, in which case the cardiac event rate in those patients with transient ischemic dilation and normal perfusion in the Abidov study would be expected to be higher. This discrepancy suggests that the pathologic process leading to the presence of transient ischemic dilation is not always related to macrovascular CAD alone.

The mechanism of transient ischemic dilation remains controversial and may in fact be due to more than one pathologic process. Although there is some evidence that physical left ventricular dilatation can occur with ischemia (11,12), it is generally accepted that transient ischemic dilation is most likely an apparent phenomenon due to subendocardial ischemia (8,9,20) or systolic dysfunction of the left ventricle (13). Evidence for this belief comes from both the scintigraphic and the echocardiographic measurement of the ventricular parameters immediately after stress or during stress. Iskandrian et al. (9) demonstrated a 30% increase in the cavity area of the endocardial border, compared with only a 6% increase in the cavity area of the epicardial border. Van Tosh et al. (13) used echocardiography to examine patients with and without transient ischemic dilation seen on scintigraphic imaging. They found that the rest and stress echocardiographic end-diastolic area did not change in patients with transient ischemic dilation, suggesting that the scintigraphic manifestations were due to systolic dysfunction of the left ventricle. Takeishi et al. (8) showed that stress and rest end-diastolic left ventricular volume and ejection fraction were unchanged among patients with transient ischemic dilation, also supporting the concept of subendocardial hypoperfusion. The loss of tracer uptake in the hypoperfused inner endocardial border on the poststress images may produce an effect of apparent thinning and therefore the impression of cavity enlargement.

There are limited data implicating LVH in the etiology of transient ischemic dilation. Sugihara et al. (21) studied 50 patients with hypertrophic cardiomyopathy and compared them with 20 healthy controls using ^{201}Tl SPECT. They found a high prevalence of transient ischemic dilation in patients with hypertrophic cardiomyopathy and theorized that this finding was based on diffuse subendocardial hypoperfusion. Robinson et al. (22) also found transient ischemic

dilation in patients with hypertensive heart disease and LVH by thallium or electrocardiographic criteria. We found that 18% of our patient cohort had LVH by echocardiographic criteria. These patients demonstrated a higher incidence of transient ischemic dilation in the presence or absence of severe CAD, supporting the argument that other pathophysiologic factors besides the presence of angiographically severe CAD play a role in the development of transient ischemic dilation. More than likely, a greater reduction in subendocardial perfusion than in transmural perfusion develops in hypertrophied myocardium, generating apparent dilatation at lower levels of quantifiable ischemia.

To our knowledge, this is the first time that diabetes mellitus has been shown to be an independent predictor of transient ischemic dilation. Furthermore, in this study diabetes was a stronger independent predictor of transient ischemic dilation than was the presence of either severe CAD or ischemia, possibly because of the presence of undetected diffuse atherosclerosis or of coronary flow reserve abnormalities related to microvascular disease (23,24).

Both LVH and diabetes may affect coronary flow reserve in the absence of macrovascular CAD (24,25). In LVH, a relative decrease in capillary density within the hypertrophied muscle leads to coronary flow reserve abnormalities that can cause myocardial ischemia even in the absence of large-vessel CAD. In the presence of CAD, coronary flow reserve abnormalities may exacerbate the severity of ischemia (7,25). We hypothesize that, in patients with LVH or diabetes, the relatively compromised resting subendocardial perfusion, with or without severe CAD, may lead to a greater reduction in endocardial radiotracer uptake during stress and a greater apparent increase in left ventricular cavity size on poststress images.

This study demonstrated that the presence of either LVH or diabetes alters both the specificity and the sensitivity of transient ischemic dilation for severe CAD. This finding may have important implications for the clinical interpretation of transient ischemic dilation in patients with known LVH or diabetes.

Because this analysis was retrospective, a bias toward selecting patients undergoing coronary angiography was possible. However the confirmation of our results by scintigraphic ischemia as well as angiographic stenoses supports an independent role of LVH and diabetes mellitus in transient ischemic dilation. Although an interval of up to 6 mo elapsed between MPI, angiography, and echocardiography, this would be expected to diminish the strength of association between LVH, angiographic stenosis, and transient ischemic dilation and is therefore unlikely to have affected the conclusions. Although we found a strong correlation between diabetes and transient ischemic dilation, the retrospective nature of this study prohibited further investigation of diabetic subgroups and of disease severity or duration. We are conducting a prospective study specifically examining these issues.

CONCLUSION

The presence of diabetes, and to a lesser extent LVH, modifies the relationship between transient ischemic dilation and severe CAD. The threshold of CAD at which transient ischemic dilation is identified on SPECT MPI is reduced. This finding may have important implications for the clinical interpretation of transient ischemic dilation in patients with known LVH or diabetes and requires prospective investigation with a larger patient cohort.

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