

The additive value of transient left ventricular dilation using two-day dipyridamole ^{99m}Tc -MIBI SPET for screening coronary artery disease in patients with otherwise normal myocardial perfusion: a comparison between diabetic and non-diabetic cases

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Abstract

The prognostic value of transient ischemic dilation (TID) has been previously confirmed; however, its clinical significance for screening coronary artery disease (CAD) with balanced ischemia, as a cause of false negative myocardial perfusion imaging (MPI), is unclear. The goal of this study was to determine the additive diagnostic value of TID ratio for screening CAD in separate subgroups of diabetic and non-diabetics with normal perfusion. *Eighty six patients* with intermediate probability of CAD who had TID more than one in the presence of otherwise normal MPI using two-day technetium-99m methoxy isobutyl isonitrile (^{99m}Tc -MIBI) single photon emission tomography (SPET) and dipyridamole stress (summed stress score <3 and left ventricular cavity <90mL) were included in a prospective cohort study comprising two subgroups of diabetic and non-diabetic patients. An inclusive work-up with multiple noninvasive tests was performed for all patients from whom 38 cases subsequently underwent coronary angiography and 48 cases were categorized in the group with a very low likelihood (<5%) of CAD on the basis of clinical and paraclinical data over a minimum of 18 months follow up. The TID ratio was calculated using automated software. Gensini score (GS) as an indicator of severity/extent of stenosis and coronary artery index (CAI) as the number of arteries with more than 50% narrowing were calculated based on angiographic findings. *Our results showed* that only in diabetic patients with three-vessel disease, TID ratio (1.47 ± 0.23) differs significantly from the other groups of CAD. In diabetic patients subgroup, TID ratio correlated strongly with GS ($r=0.957$, $P<0.0001$) and CAI ($r=0.659$, $P=0.001$), while such correlations were not seen in the non-diabetic patients. On the basis of receiver operating characteristic curve analysis for screening CAD in diabetic patients with normal myocardial perfusion, 100% sensitivity and 77.8% normalcy rate were achieved when TID more than 1.16 was regarded as abnormal. No distinct cut-off value for abnormal TID was obtained in the non-diabetic patients. *In conclusion*, TID in diabetic patients without regional myocardial perfusion abnormality is an important sign of CAD especially when TID ratio exceeds 1.16. The higher TID ratio in these cases may predict increasing possibility of severe and extensive CAD. The value of TID in non-diabetic patients with otherwise normal MPI is not clearly determined.

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Introduction

Transient ischemic left ventricular dilation on myocardial perfusion imaging (MPI) was first described with thallium-201 chloride ($^{201}\text{TlCl}$) by Stolzenberg in 1980 and was suggested as an indicator of ischemic disease [1]. This term refers to a significant enlargement of left ventricular (LV) size on the stress compared with the rest images. Subsequent reports confirmed that transient ischemic dilation (TID) ratio correlated with severity and extent of coronary artery disease (CAD) [2, 3]. The pathophysiology of TID is still controversial and has been explained by two possible theories such as pseudo-dilation due to diffuse subendocardial ischemia [4-7] and true-dilation resulting from stress-induced stunning and/or systolic dysfunction [1, 2, 5, 8-10]. Most of the studies for evaluating the importance of TID in risk assessment of CAD are performed based on ^{201}Tl imaging [1, 2, 11-15], dual-isotope techniques [6, 16, 17] or single-day methods with ^{99m}Tc -labelled radiopharmaceuticals [18-22]. Although, myocardial stunning and diffuse ischemia as the main causes of TID occur mainly after exercise or dobutamine stress tests, dipyridamole and/or adenosine may also be capable of producing such effects in the patients with ischemic heart disease [7, 23-26]. Thallium-201 allows an earlier imaging after pharmacological stress and seems to be more suitable than technetium-99m (^{99m}Tc) for detecting stress-induced myocardial dysfunction or stunning [11]. However, pharmacological stress-induced stunning after dipyridamole injection may be induced several minutes, hours or even days after stress [23-26], allowing the two-day dipyridamole stress-rest protocol with ^{99m}Tc -MIBI to show stunning effect on the delayed images and to be capable of showing TID in patients with severe or high risk ischemia [27].

The calculated cut-off values for abnormal TID ratios in previous reports vary considerably from 1.012 to 1.4 due to group variations, radiotracers, imaging protocols (single- or two-day, gated or non-gated), types of stress and even the time of image acquisition after stress [15-17, 21, 22, 27, 28]. In most of these studies, the upper normal limit of TID ratio, as a cut-off threshold for an abnormal value, has been calculated based on mean plus two standard deviations of TID from a Gaussian distribution in populations of patients with normal MPI and low likelihood of CAD (<5%). The major drawback for most of the above mentioned studies is that, the populations studied were not prospectively evaluated either by coronary angiography or long-term follow up using alternative noninvasive modalities. In addition, most studies concerning the value of abnormal TID ratio have been conducted irrespective of the presence or absence of myocardial perfusion abnormalities [29-31]. Indeed, only a small fraction of the studied subjects had normal or near-normal MPI. In only one retrospective study, the prognostic value of TID in a large group of patients with an otherwise normal MPI based on a dual-isotope ($^{99m}\text{Tc-MIBI}/^{201}\text{Tl}$) single-day protocol has been evaluated [6] but due to inherent differences in characteristics of the isotopes the results of this study may not be applicable to the commonly used single-isotope ($^{99m}\text{Tc-MIBI}$) two-day protocol.

As a note, in many nuclear medicine departments, the patients with "near-normal" perfusion and borderline LV cavity size are being reported as normal, while they may have significant multi-vessel diseases, particularly under special conditions like diabetes mellitus causing "balanced ischemia" and false negative MPI on perfusion analysis alone. In fact, these patients could have insignificant abnormality or transient left ventricular dilation that is not distinguished from "perfectly normal" scan. In the present study, using a gold standard reference reported on invasive angiography and prospective long-term multiple noninvasive assessments, we evaluated whether or not TID ratios have an additive diagnostic value for effective screening of CAD in patients with "apparently normal" or "near-normal" MPI.

Subjects and methods

Study population

In an outpatient setting, 720 consecutive patients with pretest intermediate probability of CAD [32] who had no history of active asthma, severe obstructive pulmonary disease, clinical or electrocardiographic evidence of high degree atrio-ventricular blocks, left bundle branch block, myocardial infarction (MI), echocardiographic evidence of cardiomyopathy, valvular heart disease or experience of extensive work-up for the diagnosis of CAD underwent MPI with dipyridamole stress for diagnostic purposes. Following MPI, 411 cases with apparent abnormal myocardial perfusion or abnormal resting LV chamber size (more than 90ml) and 216 cases with TID less than 1.01 were excluded from the study. From the remaining 93 cases who fulfilled all inclusion criteria (no significant perfusion defect, no resting LV dilatation and TID more than 1.00), 86 patients signed the informed consent forms and were enrolled in this prospective study. The referring physicians requested multiple noninvasive testing for screening CAD according to our predetermined criteria. The patients and their cardiologists agreed that TID measurements would not influence the decision of whether or not to perform

invasive angiography, so the TID values were not included in the MPI reports. At arrival, the patients were divided into diabetic and non-diabetic subgroups. The definition of diabetic patient was on the basis of documented history including multiple blood glucose laboratory tests and requirement for oral anti-diabetic drugs and/or insulin.

Image acquisition

Patients fasted for at least 4h before the pharmacological stress. Consumption of nitrates, caffeine containing drugs or foods and long-acting aminophylline were terminated for at least 24h before the dipyridamole pharmacological stress. The standard pharmacological stress was carried out with intravenous injection of 0.56mg/kg dipyridamole over a 4min period. Whenever the patient showed dipyridamole side effects such as vertigo, chest pain, headache and electrocardiographic changes, 250mg aminophylline was slowly injected intravenously 5min after radiotracer injection.

A MIBI kit (manufactured by Atomic Energy Organization of Iran, Tehran, Iran) was used and standard labeling with ^{99m}Tc was performed according to the manufacturer's instructions. A dose of 666-814MBq was given 4min following stress. A standard acquisition protocol with SPET was performed about 60min after radiotracer injection, using a rotating, dual head gamma camera (Solus, ADAC, Milpitas, CA) equipped with a low-energy high resolution parallel hole collimator. A 15% window around the 140keV photo peak was used. During the image acquisition, patients were supine in position. Thirty-two projections at 30sec were obtained over a 180-degree circular orbit, from 45 degrees right anterior to 135 degrees left posterior oblique on a 64×64×16 matrix and 38.5cm detector mask. Rest phase study was carried out with a similar imaging protocol in the following day.

Image analyses and interpretation

Pegasys software (ADAC system) was used for reconstruction of the images. Cine-display of the rotating planar projections was reviewed to assess sub-diaphragmatic activities, attenuations and patient motion to recheck technical quality of the images. The raw data were reconstructed using ramp and Butterworth filters with a window frequency cut-off of 0.45 and order of 9. The reconstructed data were quantitatively processed using a commercially available automated program, Auto-QUANT software package (Cedars-Sinai Medical Center). Summed stress score (SSS), summed rest score (SRS), summed difference score (SDS), TID ratio and LV chamber sizes on stress and rest images were measured. As mentioned above, a chamber size equal or less than 90mL, SSS less than 3 and TID more than 1.00 were considered as inclusion criteria for the study.

Follow up and angiographic assessments

All patients were actively followed within a course of at least 18 months duration. The follow up after MPI was 646±185 (474-1067) days. The subsequent clinical situations, the findings of exercise tolerance test, echocardiography and laboratory test results including serum glucose and complete serum lipid profiles were recorded. Thirty eight patients whose likelihood of CAD didn't change from the subgroup of intermediate at the beginning to that of low probability during subsequent

follow-ups [33], underwent coronary angiography under the care of an expert cardiologist (DKH). Significant CAD was defined as at least 50% stenosis in one or more main coronary arteries or their major branches.

Forty eight patients were finally judged to have a very low (5%) likelihood of CAD toward the end of follow-up using "Bayes' theorem" and conditional analysis of post-test probability on the basis of multiple noninvasive workups [33, 34]. Finally, the patients with "very low likelihood" of CAD and the patients showing normal angiograms were considered as negative for the presence of significant CAD.

The extent and severity of CAD was evaluated by "Coronary artery index" and "Gensini score" [35]. "Coronary artery index" was the number of vessels with significant stenosis. Scores ranged from 0 (negative for CAD on angiography or less than 5% likelihood of CAD over the period of follow up) to 3, depending on the number of vessels involved. "Gensini score" grades the severity and extent of CAD incorporating the degree and location of intra-luminal stenosis. In this scoring system, the degrees of stenosis in the coronary arteries are 0 for no narrowing, 1 for 1%-25% narrowing, 2 for 26%-50% narrowing, 4 for 51%-75% narrowing, 8 for 76%-90% narrowing, 16 for 91%-99% narrowing, and 32 for complete occlusion. This score was then multiplied by a factor that copes with importance of the lesion's position in the coronary arteries, for example 5 for the left main coronary, 2.5 for the proximal left anterior descending (LAD) and proximal left circumflex (LCx), 1.5 for the mid-region of the LAD, 1 for the distal LAD, the first diagonal, the proximal, mid and distal region of the right coronary artery (RCA), the postero-descending, the middle and distal region of the LCx coronary arteries (2 for both of them if LCx artery is dominant) and the optus marginalis, and 0.5 for the second diagonal and the posterolateral branch. The "Gensini score" was expressed as the sum of the scores for all coronary arteries.

Statistical analysis

All statistical analyses were performed using SPSS version 14 (SPSS Inc.). Continuous variables are shown as mean±SD. Nominal by nominal, nominal by ordinal and ordinal by ordinal categorical variables were compared with χ^2 , Eta and Gamma statistical tests, respectively. The TID ratios of normal coronary, single, two and three vessel CAD were compared with a non-parametric analogue of one-way analysis of variances (Kruskall-Wallis H test). Spearman Rho correlation coefficient analysis was used to identify relationship between TID and severity or extent of CAD as stated with coronary artery index or Gensini score. To assign the best cut-off value of abnormal TID ratio for identifying single- or multi-vessel CAD, receiver operating characteristic (ROC) curve analysis was used. The data were considered statistically significant with $P < 0.05$.

Results

Baseline characteristics of studied population are summarized in Table 1. No significant difference between diabetic and non-diabetic patients was observed as far as the baseline variables such as age, gender, hypertension, smoking and rest ventricular volume were concerned. Hyperlipidemia was the only factor differed between the two groups.

Follow up assessments

The incidence of documented CAD in overall population of patients with TID more than 1.0, normal perfusion and

Table 1. Baseline characteristics of studied population.

Variable	Diabetic (23 cases)	Non-diabetic (63 cases)	Overall	P
Age (year; mean ± SD)	56.91 ± 9.19	55.86 ± 11.60	56.14 ± 10.96	0.695 NS
Sex				
Female	20/23	46/63 (73%)	66/86	0.176 NS
Male	3/23 (13%)	17/63 (27%)	20/86 (23.3%)	
Hypertension	16/23 (69.6%)	31/63 (49.2%)	47/86 (54.7%)	0.093 NS
Smoke	4/23 (17.4%)	11/63 (17.5%)	15/86 (17.4%)	0.994 NS
Hyperlipidemia	16/23 (69.6%)	15/63 (23.8%)	31/86 (36%)	<0.0001 S
Rest ventricular volume (ml)				
<35	12/23(52.2%)	20/63 (31.7%)	32/86 (37.2%)	0.083 NS
35-90	11/23 (47.8%)	43/63 (68.3%)	54/86 (62.8%)	

SD: Standard deviation; NS: Non-significant; S: Significant

normal rest LV cavity size was 21/86 (24.4%). Among 21 patients with CAD, 12 (57.1%) had multi-vessel and 9 (42.9%) had one-vessel disease. Three cases (3.49%) experienced a nonfatal cardiac event in the first year of follow-up and were confined to bed for more than 3 days in the coronary care unit (CCU), one non-diabetic male with TID=1.23 and severe three vessels CAD and two diabetic females with TID of 1.17 and 1.26 both revealed multi-vessel CAD upon angiography.

No statistical difference was noted between proportional frequency of documented macro-vessel CAD in diabetic (5/23, 21.7%) and non-diabetic patients (16/63, 25.4%, $P=0.569$). The comparison between TID ratios based on the extent of CAD is shown in Table 2. The overall TID ratios were not different between diabetic and non-diabetic cases ($P=0.324$). However, in the diabetic patients, TID ratio was significantly greater in cases with three-vessel CAD, as compared to those with no CAD, single- or two-vessel CAD

A significant correlation was noted between TID ratio and Gensini score in diabetic patients ($r=0.957$, $P < 0.0001$; Fig. 1). Also a correlation was seen between TID ratio and coronary artery index in diabetic patients ($r=0.659$, $P=0.001$; Fig. 2), while no correlation was noted between TID ratio and Gensini score ($r=-0.364$, $P=0.115$) or between TID ratio and coronary artery index ($r=0.055$, $P=0.595$) in non-diabetic cases.

ROC curve analyses

The area under the ROC curve for total cases was 0.653 ± 0.08 that is different from the area under diagonal

line (P=0.036; Fig. 3). The best cut-off threshold of abnormal TID for screening CAD in the overall studied population (the patients with normal perfusion and TID

more than 1.0) is 1.17 representing 66.7% sensitivity (14/21) and 70.8% (46/65) specificity.

Table 2. Comparison of TID ratios based on the final diagnosis in diabetic and non-diabetic patients.

	Final coronary results										P value
	Normal or low likelihood		One-vessel CAD		Two-vessel CAD		Three-vessel CAD		Overall		
	N	TID ratio	N	TID ratio	N	TID ratio	N	TID ratio	N	TID ratio	
Diabetic	18	1.13 ± 0.07	0	-	1	1.17	4	1.47 ± 0.23	23	1.19 ± 0.17	0.007 S
Non-diabetic	47	1.15 ± 0.09	9	1.18 ± 0.01	5	1.14 ± 0.07	2	1.14 ± 0.13	63	1.15 ± 0.09	0.721 NS
Overall	65	1.15 ± 0.09	9	1.18 ± 0.10	6	1.15 ± 0.07	6	1.36 ± 0.25	86	1.20 ± 0.15	0.023 S

N: Number of patients; NS: Non-significant; S: Significant

It means that 14 out of 21 cases (about 67%) with final diagnosis of CAD who were formerly missed as they were screened with perfusion analyses alone, would be correctly diagnosed as ischemia after taking TID ratio into account of MPI interpretation while from 65 cases in normal or low likelihood subgroup without evidence of CAD who were firstly defined as normal MPI, 46 (70.8%) would be ultimately stay normal as well, following consideration of TID.

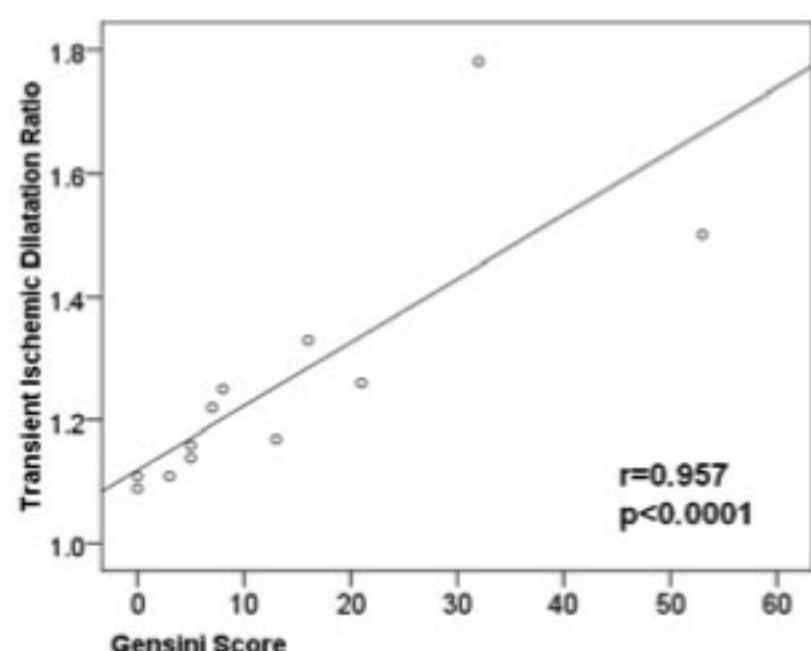


Figure 1. Correlation between transient ischemic dilation ratio and Gensini score in diabetic patients.

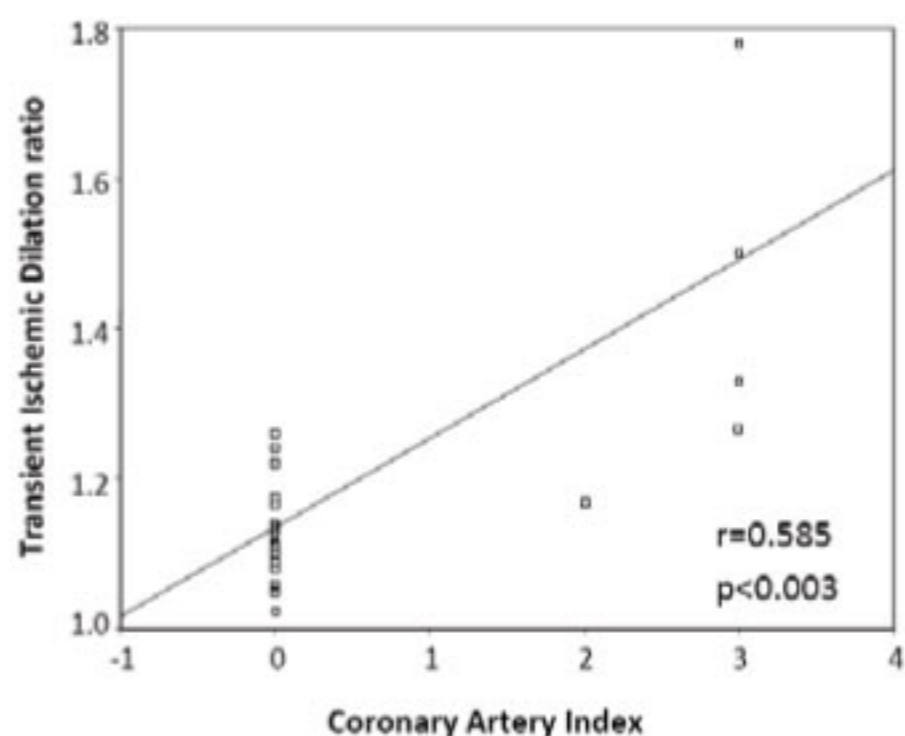


Figure 2. Correlation between transient ischemic dilation ratio and coronary artery index score in diabetic patients.

Also a significant difference between the area under the curves for diabetic and non-diabetic cases (0.950±0.049 vs. 0.555±0.095, P<0.05; Fig. 3) was

found, pointing to the fact that TID ratio in the diagnosis of CAD among patients with otherwise normal myocardial perfusion scan is more accurate in the subgroup of patients with diabetes mellitus. The analyses resulted in 60% sensitivity with 100% specificity at the TID ratio of 1.29, or 100% sensitivity with 77.8% specificity at the TID cut-off point of 1.16 in diabetic patients. This analysis also showed that the best balance between sensitivity and specificity for diabetic patients would be obtained with TID at the threshold of 1.16. On the other hand, an area of 0.555 below the curve in non-diabetic cases was not significantly different from the area under the diagonal line (P=0.512) that means TID ratio is not valuable for screening of CAD in non-diabetic patients with otherwise normal myocardial perfusion.

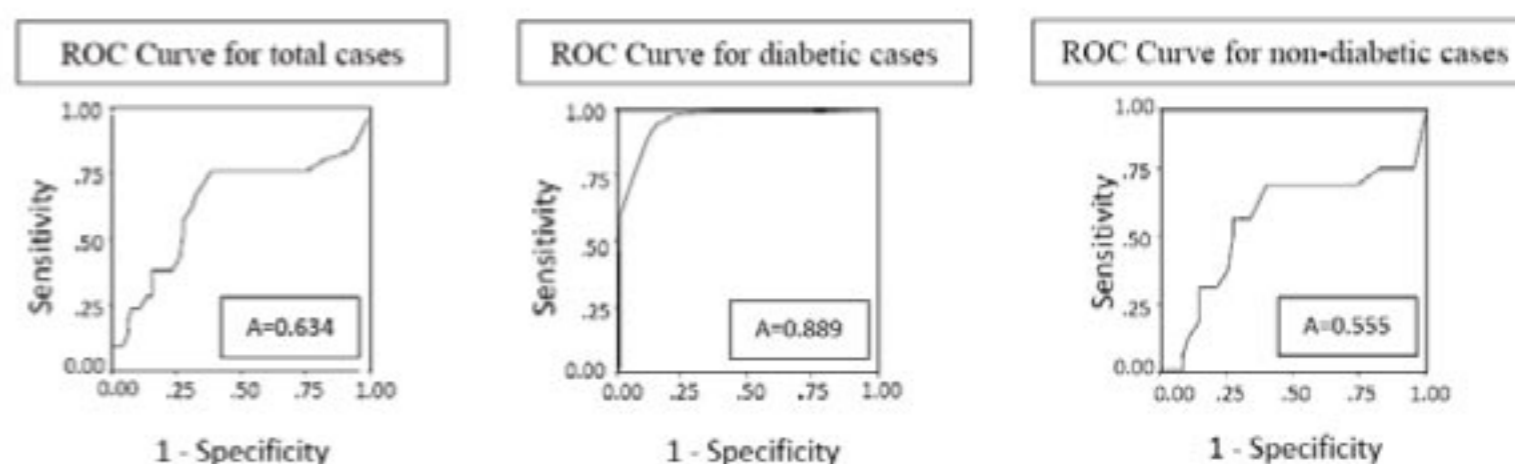


Figure 3. Receiver operating characteristic (ROC) curves for the diagnosis of coronary artery disease based on transient ischemic dilation in total (left), diabetic (center) and non-diabetic (right) patients with normal myocardial perfusion scan. (A: Area under the curve).

Discussion

TID of the left ventricle is a marker of severe and extensive CAD and has been shown to be an indicator of poor prognosis in these patients [2, 15, 16, 29, 30, 36]. The prognostic value of TID in patients with “near normal” MPI has been defined in a study by Abidov et al [6]. However, the additive value of TID in patients with otherwise normal MPI for diagnostic purposes has not yet been evaluated. In addition, in most of the previous studies [11, 21, 27, 37], the normal upper limit of TID has been determined based on calculation of mean +2SD or highest quartile in general population or in patients with low likelihood of CAD while the optimal threshold for abnormal TID has been determined or validated only in

few studies with the patients undergoing coronary angiography or long term prospective follow up [6, 16, 18]. As to our knowledge, the present study is the first one that prospectively evaluated and documented the significance of TID ratio in order to help accurate screening of CAD in the separate subgroups of diabetic and non-diabetic patients with otherwise normal dipyridamole-stress ^{99m}Tc -MIBI MPI, along with a long-term multiple noninvasive work-up and/or coronary angiography.

The overall cardiac event rates in the patients with normal MPI are usually less than 1.2% [6, 38-42], while an increased cardiac event rate of 2.4% per year has been reported in patients with normal perfusion and abnormal TID [6]. In all cases of our study, with normal myocardial perfusion and TID more than 1, the one-year total cardiac event rate was 3.5%. This higher rate may be justified possibly with the increasing chance of CAD in the patients with TID more than 1. This matter is supported by a relatively high frequency of significant CAD in all patients of our study (21/86, 24.4%) showing normal perfusion and TID>1.0. The more common CAD in patients with normal perfusion and slightly elevated TID may, in turn, be explained by "balanced ischemia" that could be missed by myocardial perfusion analysis alone. A similar finding was also found in another study with a limited number of patients who underwent coronary angiography representing more common CAD in the cases with normal MPI and abnormal TID than in the group with both normal MPI and TID ratio [6].

With respect to the above evidences, in order to diagnose CAD, TID analysis combined with myocardial perfusion assessment may represent a lower false negative rate. This matter was also investigated by others [8, 16, 27]. Although, a significant correlation between the extent/severity of perfusion defects (as measured by SSS) and TID ratio has been reported by several authors [16, 27], some discordant findings between SSS and TID assessments have also been reported especially in cases with mild perfusion defects [16]. A "balanced ischemia" due to multiple vessel or diffuse small vessel diseases involving all myocardial regions may provide explanation for the occurrence of more severe TID in the presence of lower SSS or "near normal" perfusion [8]. Thus, the TID ratio has been considered by some authors to have a potential additive value in the diagnosis of CAD, especially in cases with discordance between SSS and TID [16]. However, these authors used different isotopes for stress and rest phases leading to a complexity in evaluating LV volumes and TID ratio. Furthermore, only a small number of cases with SSS<4 (28 cases) were evaluated in their study, of whom only a small fraction was assessed by angiography. Accordingly, their data were appropriate to assess TID values for prognostic purposes and to predict the future cardiac events. However, since they did not have a gold standard for diagnosis of CAD in all patients, it was not possible to assess the additive value of TID for screening purposes. This limitation was not a major problem in our study.

Using the threshold of 1.17 for abnormal TID in all our patients, 14 out of 21 cases (67%) with CAD who were formerly missed using perfusion analyses alone, were correctly diagnosed as ischemia while, from 65 cases without evidence of CAD who were originally defined as normal on MPI, 46 (70.8%) would be ultimately stay normal as well, but 19 cases (29.2%) were falsely positive. Thus, TID ratio may identify more patients with CAD, which may have been underestimated

by analysis of perfusion defects alone. Normalcy rate however, might be decreased with increasing false positive results in these patients. Choosing this policy may give rise to some unnecessary invasive coronary angiography but this shortcoming would be overshadowed by decreasing the number of undiagnosed patients with high risk of cardiac events. This concern would be highlighted while considering the fact that almost two-third of patients with CAD had multi-vessel disease and all cardiac events in our study occurred in cases with multi-vessel CAD. "Balanced ischemia" is specially a major challenge in diagnosis of multi-vessel or micro-vessel disease particularly in high risk situations such as diabetes mellitus. Diabetes is one of the strongest independent predictors of TID on MPI of the patients suspected to have CAD, which is even stronger than severity of CAD [20]. In the presence of three-vessel CAD in our studied population, the mean TID value rose from 1.14 ± 0.13 in patients without diabetes to 1.47 ± 0.23 in patients with diabetes. A comparable finding, i.e. a higher incidence of TID in diabetic than non-diabetic patients in the presence of severe CAD; 54% vs. 21%, $P<0.004$ has been reported [20]. The authors found that diabetes may increase the incidence of TID, independent to the presence of angiographically proven severe CAD and there might be another factor in diabetic patients along with severity and extent of CAD, affecting TID ratio. This finding raised doubts about the predictive value of TID for diagnosis of severe macro-vessel CAD in the presence of diabetes [20]. Although the results of their study are to a great extent comparable with our findings, their conclusion could be further discussed. To deal with this important issue, and answer the question about the predictive value of TID for the diagnosis of severe CAD in diabetic patients, we considered three major different aspects of design in the present study. In the above study, the patients were evaluated regardless of perfusion status [20], while in our present study only patients without obvious perfusion abnormality on MPI were included. Also, due to the retrospective design of the above study, the ethical consideration for submitting the patients with a fair suspicion of CAD to perform invasive coronary angiography might induce an unavoidable bias toward selecting the patients for the study [43-45]. The degree of this bias is reflected on the frequency of normal and abnormal angiographies. Since, only 55.3% of our studied patients had angiographically proven significant CAD, we are confident that there was a lesser degree of this type of bias in our study [33]. In addition, the diabetic and non-diabetic patients may have different threshold of abnormal TID and the abnormal cut-off value calculated based on general population may not be applicable to this subgroup with diabetes mellitus. To compare abnormal TID ratio of diabetic and non-diabetic patients, we should prohibit the influence of interfering factors. The diabetic and non-diabetic patients in our study were comparable because distributions of confounding variables such as other major risk factors (except for hyperlipidemia) or interfering factors such as age, gender and resting LV cavity size were comparable in both subgroups (Table 1). In diabetic patients of our study, a significant correlation was noted between TID ratio (as an exclusive criteria indicating extent of ischemia in patients with otherwise normal MPI) and the number of abnormal vessels or Gensini score (as angiographic indicators of severity and extent of CAD), while such correlations was not seen in non-diabetic cases. Poor control of blood glucose in diabetes may lead primarily to

diffuse micro-vessel damage and may cause TID originating from a diffuse subendocardial ischemia [20]. This conclusion was confirmed by a study evaluating the correlation between glycosylated hemoglobin (HbA_{1c}) and TID [46]. According to this study, diabetes and its long term inadequate control could be a factor that affects TID ratio; however, unfortunately, their results have not been supported by angiography or long-term follow-up, therefore, the exact cause of TID is still doubtful. In the present study, despite normal myocardial perfusion, a strong association between TID and severity of macro-vessel disease (Gensini score) was observed in diabetic patients. The combination of severe macro- and micro-vessel disease in diabetics may lead to higher TID ratios as a result of balanced subendocardial ischemia throughout myocardium.

A 100% sensitivity with 77.8% specificity for the test was obtained at the TID cut-off point of 1.16 in the diabetic patients. This threshold point in diabetic patients with normal myocardial perfusion is equivalent to assuming that all cases with equal or less than this value have low likelihood of CAD or would have minimal risk of cardiac events in the future. Alternatively, a cut-off point of 1.29 for abnormal TID ratio suggests that all cases with more than this value have significant CAD. On the other hand, using a distinct cut-off value does not appear to be a proper approach in the diagnosis of CAD in non-diabetic cases with normal perfusion. In these cases, the TID ratio should be evaluated conservatively by regarding the whole clinical setting into consideration.

Limitations of the study

The number of patients in our study was limited and this limitation would not permit us to do multivariable prognostic analysis to predict the long-term adverse outcome, more accurately. Ethical limitations of performing angiography for all patients and the cost of multiple-test work-up were also among the limiting factors. The advantages of this study are that it was a prospective study conducted in a fairly appropriate number of patients followed in a single center with a quite inclusive and long-term work-up program.

In conclusion, the interpretation of MPI should be combined with TID values, especially in diabetic patients with intermediate pretest probability of CAD and near normal myocardial perfusion scan (SSS<3). By this approach, it is recommended that in diabetic patients with TID>1.16, the scan can be reported as positive for balanced ischemia even in the presence of normal myocardial perfusion. The higher TID ratio in these cases may predict increasing possibility of severe and extensive CAD. This approach seems to be inappropriate for screening purpose, in non-diabetic patients.

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