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ORIGINAL ARTICLE

Transient ischaemic dilation ratio thresholds in patients with zero coronary calcium score undergoing exercise or dipyridamole stress SPECT myocardial perfusion imaging using a cadmium-zinc-telluride camera

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Aims Transient ischaemic dilation (TID) is a marker of underlying extensive coronary artery disease (CAD) during myocardial perfusion imaging (MPI). The cut-off for a normal TID ratio (TIDr) value is often derived from a cohort of individuals with no apparent CAD. Varying criteria have been used to define the absence of CAD. We aim to derive TIDr cut-offs using patients with normal MPI and coronary artery calcium (CAC) score of zero, and compare the TIDr obtained from different software packages.

Methods and results We studied 232 patients with zero CAC and normal MPI undergoing exercise or dipyridamole stress using either a 1- or 2-day protocol. All patients were scanned in the supine position with a cadmium-zinc-telluride camera. TIDr was automatically generated using quantitative perfusion SPECT (QPS) software initially, and subsequently using Myometrix for comparison. The TIDr cut-offs calculated using the mean + 2 standard deviation were 1.29 and 1.24 for the 1- and 2-day protocol groups, respectively. In patients undergoing a 2-day protocol, dipyridamole stress resulted in significantly higher mean TIDr when compared to exercise stress (1.07 ± 0.13 vs. 1.01 ± 0.12, $P = 0.035$). Myometrix-derived TIDr were also significantly lower compared to QPS-derived values for most protocols except for 2-day exercise stress.

Conclusion This study is the first to derive TIDr threshold values using a normal population defined by zero CAC and normal MPI. TIDr was found to vary depending on stress modality, protocol as well as the software used.

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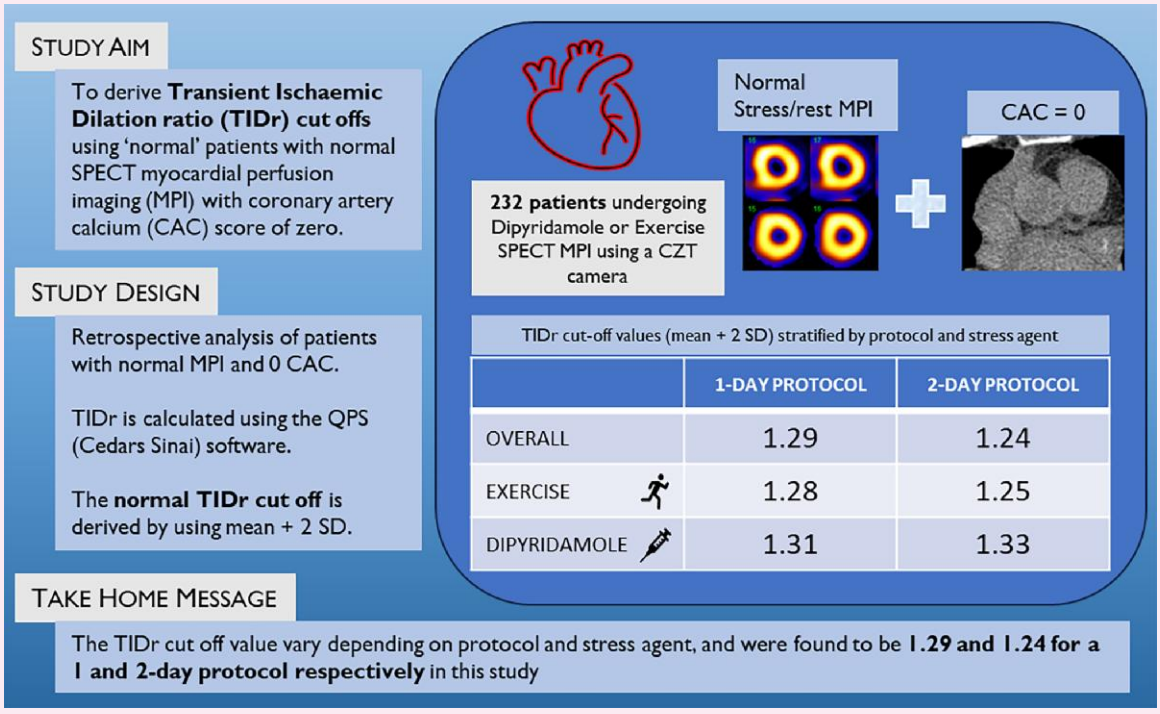
Graphical Abstract



Keywords myocardial perfusion imaging (MPI) • coronary artery calcium (CAC) • transient ischaemic dilation (TID) • TID ratio (TIDr)

Introduction

Myocardial perfusion imaging (MPI) is frequently performed for diagnosis and risk stratification of suspected coronary artery disease (CAD). Transient ischaemic dilation (TID), which is the visualization of an apparently increased post-stress left ventricular (LV) cavity size compared to rest is a marker of underlying extensive CAD.[1] This phenomenon has been attributed to global subendocardial ischaemia[2] as well as post-stress stunning.[3] TID can be quantified by the ratio of the post-stress to rest non-gated LV cavity volumes. The 'normal' TID ratio (TIDr) is known to differ between different stress agents and camera types.[4] Almost all previously published studies had derived the 'normal' TIDr thresholds using patients with normal myocardial perfusion and no prior history of CAD.[5] However, normal myocardial perfusion does not exclude underlying CAD completely as 'balanced ischaemia' can still occur.[6,7] Concurrent coronary artery calcium (CAC) scoring with MPI has been advocated as a means of detecting underlying subclinical coronary atherosclerosis.[8,9] The absence of CAC is associated with an extremely low rate of major adverse cardiac events, even amongst higher-risk individuals such as diabetics.[10,11] Conversely, any detectable CAC portends incremental risk of major adverse cardiac events.[12,13] We hypothesize that patients with zero CAC are more representative of true 'normal' patients with a very low likelihood of having underlying CAD. We therefore aim to derive the normal TIDr thresholds using a cohort of patients with normal myocardial perfusion and zero CAC. We also compare the differences between TIDr calculated from two separate software packages used for image post-processing and interpretation.

Materials and methods

Study population

We retrospectively studied all patients with a normal exercise or dipyridamole stress/rest technetium-99m (Tc-99m) tetrofosmin SPECT MPI and a CAC score of 0 performed between 2 March 2016 and 28 February 2017. Patients with known CAD were excluded. We defined normal MPI as a scan having homogeneous perfusion with a summed stress score (SSS) of 0 and post-stress LV ejection fraction (LVEF) >50% with no wall motion abnormalities (WMA) on gated images. Patient demographics and medical comorbidities were traced from electronic medical records. This study was approved by the National Healthcare Group Domain Specific Review Board (2017/00625) and the need for individual patient informed consent was waived.

Stress and imaging procedure

All patients underwent stress/rest imaging using either a 1- or 2-day protocol. In a 1-day protocol, either the stress or rest component may be performed first, in which patients received 8mCi followed by 24mCi of Tc-99m tetrofosmin for the first and second components respectively. A 2-day protocol was mandated for all patients weighing ≥ 80 kgs and was also performed for some patients due to logistic

reasons. We used 20mCi of Tc-99m tetrofosmin for each imaging, with higher doses (e.g. 25mCi) given according to actual body weight.

Stress testing was performed with either dipyridamole or exercise treadmill testing. All patients were scanned in the supine position using a cadmium-zinc-telluride (CZT) camera (Discovery NM530c, GE Healthcare). Additional post-stress prone images were also routinely acquired unless there were physical limitations or contraindications to prone positioning. Gated supine images were acquired at both post-stress and rest by dividing the cardiac cycle into eight frames. An average R–R interval of ±15% was accepted for gating. LV volumes and LVEF were calculated from the gated images. Pre-test preparation, cardiac stress testing, image acquisition and processing were performed in accordance with standard published protocols.[14] Gated non-contrast computed tomography (CT) was performed using a 256 slice dual-source CT scanner (Siemens Somatom Definition Flash, Siemens, Erlangen, Germany) with the CAC quantified using the Agatston method.[15]

Image interpretation

All MPI images were processed and reconstructed on a dedicated workstation (Xeleris, GE Healthcare, Haifa, Israel). Static perfusion and gated data were processed using Quantitative Perfusion SPECT and Quantitative Gated SPECT (QPS and QGS, respectively, Cedars-Sinai Medical Centre, Los Angeles, USA). All images were interpreted by an experienced nuclear cardiologist for the absence of perfusion defects, as defined by an SSS of 0, as well as an absence of WMA on gated images. TIDr was automatically generated using the QPS software.[16] LV volumes were also automatically generated from QGS. All contours were assessed by the nuclear cardiologist with manual adjustments made wherever necessary. For the purposes of the study, all included cases were processed again for comparison of the TIDr using MyoMetrix (GE Healthcare, Haifa, Israel).[17]

Statistical analysis

The normality of data was assessed using the Shapiro–Wilk test and Q–Q plot. Normally distributed continuous numerical values were expressed using mean with standard deviation (SD) and analysed utilizing the *t*-test. Skewed data were presented using median with interquartile range and compared utilizing the Wilcoxon–Mann–Whitney test. Categorical variables were expressed as frequencies and percentages and further tested using the $\chi 2$ test. We derived the upper reference limits of TIDr using mean +2 SD. Comparisons of the TIDr between QPS and MyoMetrix were made using the paired *t*-test. All statistical analyses were performed using IBM SPSS statistics version 16.0. Significance tests were two-sided at the 5% significance level.

Results

Baseline characteristics

A total of 232 patients underwent stress/rest SPECT MPI scans with 141 undergoing a 1-day protocol and 91 undergoing a 2-day protocol. Baseline clinical and imaging characteristics were reported in *Tables 1* and *2* for 1-day and 2-day protocols, respectively. In the 1-day protocol group, the mean age was 61.2 years and 43.3% were males. Cardiovascular risk factors included diabetes (27.0%), hypertension (53.6%), and dyslipidaemia (52.5%). Patients who underwent dipyridamole stress were significantly older (mean age 63.8 vs. 56.0, $P < 0.001$) and less likely to be male (36.2% vs. 57.4%, $P = 0.016$) compared to the group that underwent exercise stress testing.

In the 2-day protocol group, the mean age was 55.7 years and 44.0% were males. Cardiovascular risk factors included diabetes (20.9%), hypertension (50.5%), and dyslipidaemia (51.6%). Patients undergoing dipyridamole stress were again significantly older (mean age 58.2 vs. 51.9, $P = 0.006$) and more likely to be hypertensive (62.5% vs. 31.4%, $P = 0.004$).

Normal thresholds for TIDr using QPS

The TIDr, stratified by protocol and stress modality, were all normally distributed as shown in the quantile–quantile plots (*Figure 1*). The mean TIDr for a 1-day protocol was 1.03 with an SD of 0.13, giving an upper limit of a normal threshold of 1.29. The mean TIDr between the exercise and dipyridamole stress groups was not significantly different (*Table 1*). The mean TIDr for a 2-day protocol was 1.02 with an SD of 0.11, giving an upper limit of a normal threshold of 1.24 (*Table 2*). However, the mean TIDr was significantly higher with dipyridamole stress as compared to the exercise stress group (1.07 ± 0.13 vs. 1.01 ± 0.12, $P = 0.035$) (*Table 2*).

Table 1 Baseline characteristics for patients undergoing 1-day protocol

	All *N* = 141	Exercise *N* = 47	Dipyridamole *N* = 94	*P* value
Age, years	61.2 (±10.3)	56.0 (±8.6)	63.8 (±10.1)	<0.001
BMI, kg/m^2	23.1 (±3.5)	23.4 (±3.1)	22.9 (±3.7)	0.423
Male gender	61 (43.3)	27 (57.4)	34 (36.2)	0.016
Diabetes	38 (27.0)	11 (23.4)	27 (28.7)	0.502
Hypertension	75 (53.6)	25 (53.2)	50 (53.8)	0.949
Dyslipidaemia	74 (52.5)	23 (48.9)	51 (54.3)	0.551
Smoking status				0.646
Non-smoker	120 (85.1)	40 (85.1)	80 (85.1)	
Current smoker	12 (8.5)	5 (10.6)	7 (7.4)	
Ex-smoker	9 (6.4)	2 (4.3)	7 (7.4)	
TID ratio	1.03 (±0.13)	1.02 (±0.13)	1.03 (±0.14)	0.796
Gated LV end-systolic volume, mls	21.3 (±12.5)	22.9 (±12.3)	20.0 (±10.7)	0.188
Gated LV end-diastolic volume, mls	63.0 (±18.2)	65.6 (±18.4)	61.7 (±18.1)	0.252
Post-stress LVEF, %	69.0 (62.0–75.5)	69.0 (61.0–75.0)	68 (62.0–76.3)	0.749
Rest LVEF, %	69.0 (62.0–75.0)	69.0 (62.0–79.0)	69.0 (62.8–74.3)	0.979

Table 2 **Baseline characteristics for patients undergoing 2-day protocol**

	All $N = 91$	Exercise $N = 35$	Dipyridamole $N = 56$	P value
Age, years	55.7 (±10.7)	51.9 (±8.3)	58.2 (±11.4)	0.006
BMI, kg/m^2	29.0 (±6.3)	27.7 (±5.1)	29.8 (±6.8)	0.137
Male gender	40 (44.0)	20 (57.1)	20 (35.7)	0.053
Diabetes	19 (20.9)	9 (25.7)	10 (17.9)	0.370
Hypertension	46 (50.5)	11 (31.4)	35 (62.5)	0.004
Dyslipidaemia	47 (51.6)	15 (42.9)	32 (57.1)	0.185
Smoking status				0.889
Non-smoker	79 (86.8)	30 (85.7)	49 (87.5)	
Current smoker	8 (8.8)	3 (8.6)	5 (8.9)	
Ex-smoker	4 (4.4)	2 (5.7)	2 (3.6)	
TID ratio	1.02 (±0.11)	1.01 (±0.12)	1.07 (±0.13)	0.035
Gated LV end-systolic volume, mls	27.6 (±14.0)	27.3 (±12.9)	27.8 (±14.9)	0.887
Gated LV end-diastolic volume, mls	76.2 (±20.3)	76.0 (±19.5)	76.4 (±21.1)	0.939
Post-stress LVEF, %	67.0 (59.8–72.0)	65.5 (59.5–72.3)	67.0 (59.0–72.0)	0.964
Rest LVEF, %	66.0 (59.0–74.0)	64.0 (60.8–74.0)	67.0 (58.0–75.0)	0.660

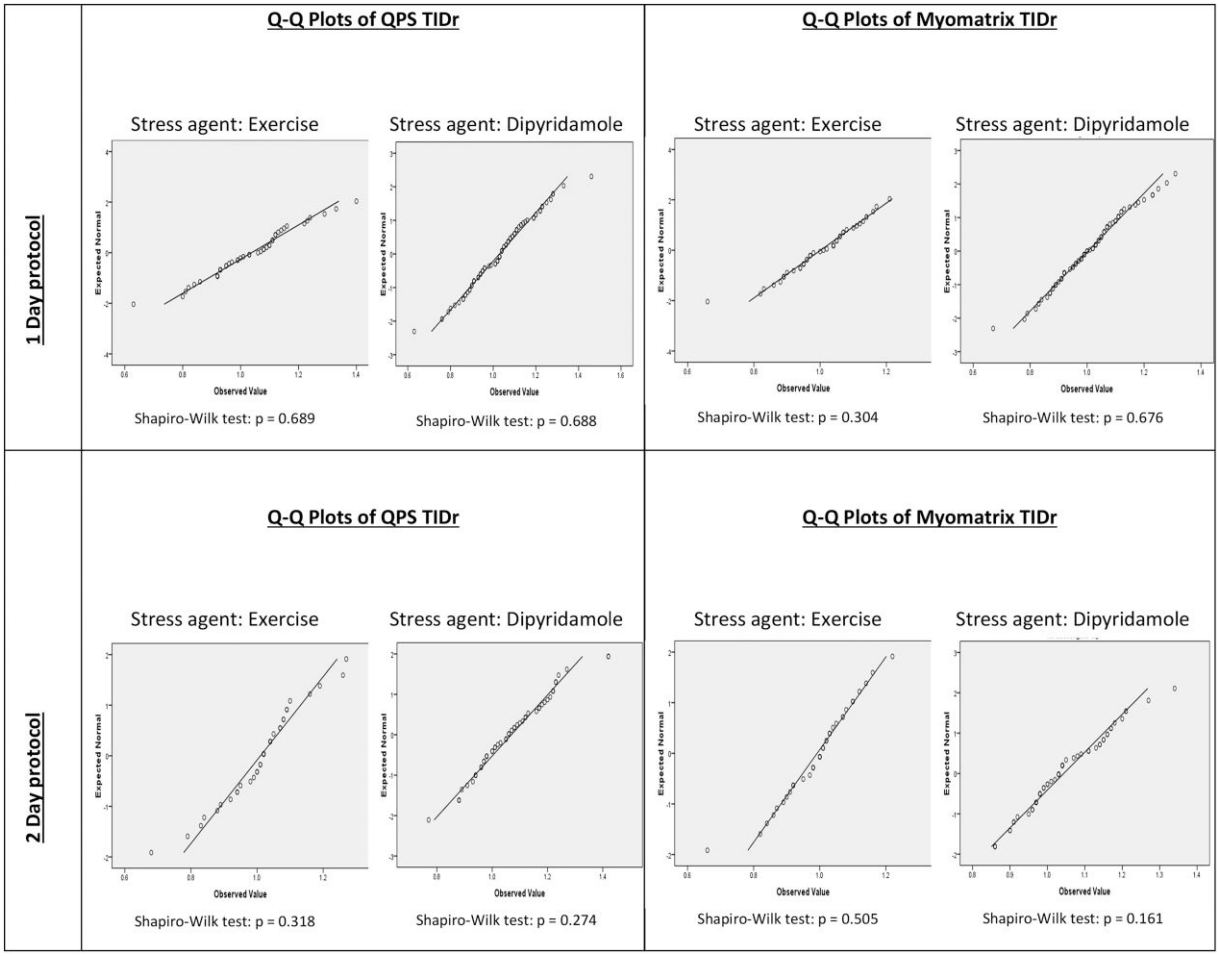


Figure 1 Evaluation of normality of TIDr in eight subgroups using quantile–quantile (Q–Q) plot and Shapiro–Wilk test.

When stratified by stress modality (*Table 3*), the mean TIDr for exercise stress was similar between the 1- vs. 2-day protocol groups (1.02 ± 0.13 vs. 1.01 ± 0.12, $P = 0.655$). The mean TIDr for dipyridamole stress was also similar in the 1- vs. 2-day protocol groups (1.03 ± 0.14 vs. 1.07 ± 0.13, $P = 0.428$).

Comparison of TIDr between QPS and Myometrix software

The TIDr derived from QPS were compared with those from Myometrix, stratified by protocol and stress modality (*Table 4*). Myometrix-derived mean TIDr were significantly lower than QPS TIDr for 1-day exercise as well as both 1- and 2-day dipyridamole protocols. Myometrix-derived mean TIDr was numerically lower than QPS TIDr for 2-day exercise stress although this was not statistically significant (0.99 vs. 1.01, $P = 0.065$).

Discussion

Using a cohort of patients with normal stress/rest MPI and CAC of 0, we derived TIDr thresholds using the mean +2 standard deviations assessed using QPS, stratified by protocol and stressor. The TIDr cut-offs for 1-day protocol were 1.28 and 1.31 for exercise and dipyridamole stress, respectively. TIDr cut-offs for 2-day protocol were 1.25 and 1.33 for exercise and dipyridamole stress, respectively. The corresponding TIDr derived using Myometrix software were significantly lower in all subgroups, except in the 2-day exercise stress protocol where statistical significance was not achieved.

TID seen during MPI was first described by Stolzenberg *et al.*[1] in 1980 as an elevated post-stress to rest LV volume ratio. Weiss *et al.* later demonstrated the association between TID seen during stress redistribution thallium-201 scintigraphy and multi-vessel critical coronary stenosis on invasive angiography.[18] Subsequently, multiple studies have shown the prognostic implications of TID as being associated with increased rates of major adverse cardiac events particularly when associated with ischaemia seen on MPI or in diabetics.[19] Apart from visual assessment, TID can be quantified objectively using the TIDr, which can be automatically generated using commercially available software such as QPS by comparing the endocardial LV volumes measured in ungated post-stress and rest short-axis images. A common method for obtaining the TIDr threshold is to determine the mean TIDr in a cohort of 'normal' patients and then setting the cut-off value at the threshold of two SD above the mean.[4] An alternative method of using the 97.5th percentile has been proposed if the TIDr of the reference cohort does not follow a normal distribution.[20]

The cut-off value for significant TIDr differs depending on variables such as stress modality, gamma camera, imaging protocol, computation software, and even patient positioning.[4] Furthermore, previous studies have used various criteria to define the 'normal' reference population. These include a low (<5%) pre-test probability of CAD,[21] SSS of 3 and below, summed difference score of 1 and below, or an expert interpretation of a normal MPI scan.[20] However, a near normal or normal perfusion does not exclude non-flow limiting CAD. Also, 'balanced ischaemia' typically from either left main or triple vessel CAD can result in normal perfusion and remains a major pitfall of MPI.[22]

Due to the limited sensitivity of MPI for subclinical CAD, combined CAC assessment with MPI has been recommended.[23] A study by Sharma *et al.* showed that patients with normal MPI and low (<216) CAC have the lowest mortality while those with normal MPI and elevated CAC had an intermediate mortality rate of 10.7% during a mean follow-up of 2.5 years.[24] Another study also found a stepwise increase in cardiac risk with increasing CAC in both normal and abnormal MPI groups, with a CAC of 100 or more portending higher rates of major adverse cardiac events despite normal MPI.[12] On the other hand, a CAC score of zero portends a very low risk of underlying CAD and confers a good long-term prognosis.[25] The application of CAC has also been recently expanded to include low-risk symptomatic patients with no known CAD as a first-line test to exclude calcified plaque and identify a low likelihood of obstructive CAD.[26] Based on the above, we aim to establish cut-off values for TIDr using a 'normal' cohort selected based on the absence of CAC.

Cut-off values in the literature for TIDr vary due to multiple factors and range between 1.16 and 1.31 as reported in a recent review.[4] Based on our cohort, we found that QPS-derived TIDr cut-off values for a 1-day protocol were similar at 1.28 and 1.31 for exercise and dipyridamole stress, respectively. The mean TIDr was not significantly different between the two groups, which may be due to statistical limitations arising from relatively small patient numbers in each group. Previous papers have demonstrated higher TIDr for pharmacological over exercise stress.[4] The reason for this is not well understood although it has been

Table 3 Comparing 1-day vs. 2-day mean TIDr stratified by stress modality using QPS

Stress modality	1-day protocol mean TIDr (std. deviation)	2-day protocol mean TIDr (std. Deviation)	*P* value
Exercise stress	1.02 (0.13)	1.01 (0.12)	0.655
Dipyridamole stress	1.03 (0.14)	1.07 (0.13)	0.428

Table 4 Differences between QPS vs. Myometrix-derived TIDr

	Exercise stress			Dipyridamole stress		
	QPS	Myometrix	*P* value	QPS	Myometrix	*P* value
1-day protocol						
Mean (SD)	1.02 (±0.13)	1.00 (±0.11)	0.034	1.03 (±0.14)	1.00 (±0.11)	<0.001
Normal TIDr threshold (mean + 2SD)	1.28	1.22		1.31	1.22	
2-day protocol						
Mean (SD)	1.01 (±0.12)	0.99 (±0.11)	0.065	1.07 (±0.13)	1.04 (±0.11)	0.008
Normal TIDr threshold (mean + 2SD)	1.25	1.21		1.33	1.26	

postulated that TIDr is smaller post-exercise stress due to an inverse relationship between TIDr and heart rate.[26] We also found significantly different QPS-derived TIDr cut-off values of 1.25 and 1.33 for patients undergoing 2-day protocol stress with exercise and dipyridamole, respectively. There is a paucity of literature specifically assessing TIDr for a 2-day protocol. Based on limited studies, the normal TIDr is found to be slightly greater in 2-day compared to 1-day rest/stress sestamibi scans, possibly due to differences in heart rate and rhythm between the days.[26] A study of patients undergoing 2-day dipyridamole Tc-99m sestamibi found the upper limit of normal TIDr to be 1.19, using automatically derived values from the Emory Cardiac Toolbox.[27] However, exercise-stress patients were not included in that study. Mandour *et al.* studied patients undergoing both 1- and 2-day protocol Tc-99m sestamibi scans, using either exercise, adenosine, or regadenoson stress. Patients were scanned using a dual-head gamma camera and image analysis was performed using the V-Quant software.[28] Based on a cohort of patients with normal perfusion, LV function, and volumes, TIDr cut-off limits of 1.16 for exercise and 1.29 for pharmacological stress were derived. The authors acknowledged that patient numbers were too small for adequate statistical analysis to produce cut-offs stratified by same-day vs. 2-day protocols.[28]

Our study also contributes to the limited literature on TIDr in patients scanned with CZT cameras. Jameria *et al.* reported a reference limit of 1.16 and 1.29 for exercise and pharmacologic normals, respectively.[21] The corresponding TIDr cut-offs were 1.18 and 1.20 in another study by Hu *et al.*[20] However, numerical differences in the TIDr between our study and the aforementioned papers are expected due to different MPI protocols. Jameria *et al.* obtained TIDr in an upright position while our patients were imaged in a supine position. Hu *et al.* studied only 1-day protocol patients while our study included both 1-day and 2-day protocols.

Software packages such as QPS use algorithms that operate in the three-dimensional space to first derive endocardial volumes bounded by the endocardial surface and the valve plane of the short axis image sets before calculating the TIDr as the ratio of post-stress to rest LV size.[29] In our study, we found that Myometrix TIDr was significantly lower than QPS TIDr for 1-day exercise, 1-day dipyridamole, and 2-day dipyridamole protocols. Although it has been shown that these two software packages differ significantly for both perfusion scores (such as SSS) and LV gated functional parameters,[30] we are not aware of any prior study directly comparing their automated TIDr. Our data further confirms that TIDr varies depending on which software application is used for automatic segmentation and analysis of the non-gated images[31] even in 'normal' cases. The overall findings of our study suggest that although TIDr is useful for quantifying TID objectively, many factors such as scan protocol, stress agent, and even software can affect the absolute TIDr. This brings to question if there can be a true 'normal TIDr' threshold, and underscores the critical importance of exercising clinical judgement when interpreting the TIDr.

There are several limitations to our study. First, this is a relatively small single-centre study performed in a predominantly Asian population that may not be representative of other patient groups. Second, the retrospective nature of the study is subject to bias as well as being highly dependent on the accuracy of clinical documentation. Third, the derived TIDr thresholds are unique for Tc-99m tetrofosmin tracer and the specific CZT camera system which may not be extrapolated to other situations. We did not attempt to derive gender-specific TIDr as this will further reduce the already small patient numbers in each subgroup and may affect the validity of the calculated mean TIDr. Finally, we had assumed that patients with a CAC of 0, SSS of 0, normal gated LVEF with no WMA are 'normal' although we were unable to confirm this on angiography. However, as it would be inappropriate to routinely obtain additional angiographic data in patients who have already had a normal MPI, the absence of CAC was the next best method to minimize the likelihood of underlying CAD in the included cases. Moreover, a large study of symptomatic patients (median pre-test probability of 22%) with CAC of 0 showed that moderate and severe stenosis on coronary CT was seen in only 1.2% and 0.5%, respectively, with close to 90% of patients having absent stenosis.[25] In this cohort of patients with CAC of 0, there was also no significant difference in the age, gender, or prevalence of risk factors such as hypertension, diabetes, dyslipidaemia, and smoking status in those with or without at least 50% stenosis on CT angiography.[25] This data suggests that a CAC of 0 excludes severe coronary stenosis with a negative predictive value of 99.5%.[25]

Conclusion

Upper reference limits of TIDr generated from QPS software were found to be 1.29 and 1.24 for a 1- and 2-day protocol, respectively, derived using a reference population comprising of patients with a CAC of zero and a normal stress/rest Tc99m-tetrofosmin MPI scanned with a CZT camera. When compared to exercise stress, TIDr for dipyridamole stress was significantly higher in patients undergoing a 2-day protocol and is numerically higher for those in a 1-day protocol. Myometrix-derived TIDr were also significantly lower compared to QPS-derived values for most protocols. Although these reference values may be useful for our laboratory, they may not be generalized or applicable in a different population setting. Instead, clinicians and imagers should appreciate the variability that is inherent in the measurement of the TIDr and should report and interpret TIDr in the appropriate clinical context. Further studies in larger cohorts of patients undergoing SPECT MPI are needed to validate these TIDr cut-offs.

Lead Author Biography

Dr Min Sen Yew is a consultant cardiologist in Tan Tock Seng Hospital Singapore. His clinical interests include nuclear cardiology, cardiac computed tomography, and cardiac magnetic resonance imaging. Apart from his clinical duties, he is also the Programme Director for the National Healthcare Group cardiology residency programme.

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Consent

The need for individual patient informed consent was waived after review by the National Healthcare Group Domain Specific Review Board.

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Conflict of interest: None declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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