Normal limits for transient ischemic dilation with ^{99m}Tc myocardial perfusion SPECT protocols

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INTRODUCTION

Transient ischemic dilation (TID) of the left ventricle—a ratio of the stress left ventricular (LV) volume to rest LV volume—on myocardial perfusion imaging has been described as a useful marker of severe and extensive coronary artery disease (CAD).[1,2] TID measurement has also been shown to have distinct prognostic value,[3] with abnormal TID indicating increased risk of myocardial infarction or cardiac death.[4] TID is currently used in clinical practice and is routinely reported by most major quantitative software packages. The mechanisms of this relative increase of measured left ventricular volume at stress have been considered to be an apparent cavity size at stress due to subendocardial ischemia, a true increase in left ventricular volume persisting at the time of post-stress imaging due to stress-induced LV stunning, or a combination of both.[5,6]

In this issue of Journal of Nuclear Cardiology®, Jameria et al.[7] study in detail the TID derivation for the scans obtained with a new Cadmium Zinc Telluride (CZT) camera in the upright position. The TID measurements have not been studied yet on these new cameras. Potentially due to an increased resolution and different imaging position, the normal TID values could differ on these new systems. In regards to image resolution, it has been suggested that TID may be unreliable in small hearts, if reconstructed image resolution is too low[2]. So how do the results presented by Jameria et al. compare to recent studies of TID? Table 1 lists several recent published reports with various ^{99m}Tc protocols, stress methods, software tools, criterions for cut-off, and definitions of normal population. Other studies have been published previously for dual-isotope protocols.[8,9] In Table 1, it can be seen that normal cut-off values obtained by Jameria et al. are in fact remarkably similar to the values reported for exercise or pharmacological stress obtained with conventional imaging systems, including one previous report of TID in patients imaged in upright position.[10] Similar to previous reports, the threshold defined as 2 standard deviations (SD) above the mean is indeed higher for the pharmacological stress studies than for the exercise studies. When comparing these recent reports, one can appreciate that there are several potential factors affecting the value of the normal threshold, such as imaging protocol, patient position, normal population definition, statistical threshold definition, and software used for TID computation. Nevertheless, despite these methodological differences, the abnormal TID cut-offs seem to be consistent across these reports.

Some technical factors should be pointed out with regards to the study by Jameria et al. Does upright position affect the results? It is hard to tell since there are no paired supine TID measurements obtained in this report. In some clinical protocols, the upright and supine images are obtained both at stress and rest and therefore such comparison could be feasible in future studies. The normal TID cut-off values do not seem to differ from these reported by other studies despite the use of CZT camera. The number of normal regadenoson cases used for the derivation of normal limits is rather low, reflecting practical difficulty, since patients with low likelihood of disease are unlikely to undergo pharmacological stress. The authors Jameria et al. utilize the average of upright and supine perfusion results for the definition of the perfusion defect used in their analyses,

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Table 1. Recent reports and normal thresholds of transient ischemic dilation (TID) with ^{99m}Tc sestamibi

Study	Protocol	Stress type	Normal reference	Software	Criterion	TID cut-off
Golzar et al.[13]	Same day rest/stress	Regadenoson	100 LLk pts	4DMSPECT	Mean + 2 SD	1.31
Lester et al.[4]	Same day stress/rest	Regadenoson	220 normals	4DMSPECT	95% percentile	1.33
Xu et al.[12]	Rest/stress	Exercise	332 LLk pts	QPS	Mean + 2 SD	1.19
Doukky et al.[10]	Same day rest/ stress upright	Exercise Adenosine	508 (exercise) 63 (pharm) LLk pts	QPS	Mean + 2 SD	1.16 (exercise) 1.22 (pharm)
Mandour et al.[17]	Rest/stress	Exercise Adenosine Regadenoson	173 (exercise) 125 (pharm) Normals	V-Quant	Mean + 2 SD	1.16 (exercise) 1.29 (pharm)
Jameria et al.[7]	Upright CZT same day rest/stress	Exercise Regadenoson	48 (exercise) 14 (pharm) LLk pts	4DMSPECT	Mean + 2 SD	1.16 (exercise) 1.29 (pharm)

LLk pts: patients with low likelihood <5% of coronary artery disease, normals: patients with normal results of myocardial perfusion imaging (definitions vary between studies) pharm—pharmacologic stress

which is not a typical method in two-position protocols. In this regard, it has been shown previously that the defect must be present in both supine and upright images for more optimal diagnosis.[11] No attenuation correction was used, however, attenuation correction was not used in any of the studies of TID presented in Table 1. This fact should be kept in mind when using TID clinically.

HOW TO USE TID CLINICALLY?

The several studies of the clinical utility of TID presented in Table 1 attempt to define the normal limits in order to then use this binary variable to help in detecting extensive/severe CAD or indicate increased risk for adverse outcomes. However, TID is not used as a solitary variable to identify extensive/severe CAD or adverse prognosis. Regarding detecting extensive/severe CAD, TID on its own has low sensitivity; however, using the combination of the presence or absence of TID and assessment of the presence and size of myocardial perfusion defect, it is possible to increase the overall sensitivity for the detection of severe disease with unchanged specificity.[12] This combination can be accomplished for example by developing specialized rules combining total perfusion deficit (TPD) and TID variables as demonstrated by Xu et al.[12]

While TID has been studied as a binary variable (present or absent), one may question whether a TID of 1.5 has the same prognostic information as TID of 1.17 (just barely above the arbitrary 2SD threshold) for a given patient. Indeed, reported lack of added value of TID for detection of severe disease with pharmacologic testing[13] could be related to the analytic deficiency of using only an arbitrary binary cut-off for TID. It is likely that a continuous variable of TID may provide a better predictor of severe/extensive CAD or patient risk. Continuous TID variable could be matched with the individual patient profile and contribute to the individual risk estimate. Thus, TID variable should not be thought of as a standalone marker with its own normal limits, but rather as a continuous measure which is optimally combined with multiple other variables. But how might such a continuous TID variable be optimally utilized in clinical practice?

The most effective method would be perhaps to create a machine learning model where a continuous TID variable is incorporated with all other key variables such as perfusion deficit, ejection fraction, clinical data, and even an imaging protocol (dual/single isotope, stress type) in the overall diagnosis or risk assessment. In such approach, there would be no need to define an arbitrary abnormal TID threshold and a continuous final probability of disease or outcome can be computed. This final computed probability can be then discretized to several categories of risk or probability of disease, rather than just assigning a normal/abnormal finding. Indeed, such holistic approach has been shown to be very promising in diagnostic[14] and prognostic[15,16] applications demonstrating a significant overall improvement of diagnostic accuracy or risk reclassification.

SUMMARY

Multiple publications have reported the normal limits of TID measurements with ^{99m}Tc SPECT MPI including exercise and pharmacological stress as well as their diagnostic and prognostic utilities. In general, the reported TID abnormal thresholds have been shown to be lower in studies with exercise stress than in studies with pharmacological stress, but otherwise the normal values of TID were similar. In all of these reports, an arbitrary cut-off value for abnormal TID was used for either diagnostic or prognostic purposes. However, TID should be used in combination with other imaging and clinical variables. Continuous TID measure could be utilized efficiently by machine learning models, allowing more precise overall risk or diagnostic stratification, and obviating the need for arbitrary TID cut-offs.

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Disclosure

Cedars-Sinai Medical Center receives royalties for the quantitative assessment of function, perfusion, and viability, a minority portion of which is distributed to some of the authors of this manuscript (Guido Germano and Piotr J. Slomka).

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