Comparison of transient ischemic dilation ratios in SPECT and SPECT-CT myocardial perfusion imaging in the low pre-test probability group

Original Article

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ABSTRACT

Introduction: The main purpose of this study was to compare transient ischemic dilation (TID) ratios in SPECT-low dose CT and SPECT Myocardial Perfusion Imaging (MPI) by application of different quantitative programs and quantify the possible shift in the upper normal limits of TID ratio in the SPECT-CT MPI.

Methods: 149 Patients with low pre-test probability for coronary artery disease (CAD), based upon Diamond and Forrester method entered the study. Each patient underwent both attenuation correction (AC) SPECT-CT MPI and non attenuation correction (NAC) SPECT MPI (two day Tc-99m sestamibi stress-rest protocol). Normalcy rates were also calculated and compared. The comparison was based on both visual interpretation and quantitative analysis.

Results: In the low pre-test probability group visual interpretations lead to a statistically significant improvement in normalcy rate in the SPECT-CT acquisition compared to the SPECT MPI. Regardless of the stress type and software programs used, no significant difference was noted in the upper normal limits of the TID ratios between the AC and NAC acquisitions.

Conclusion: The study showed superiority of SPECT-CT MPI to SPECT MPI in terms of normalcy rate. We also propose new upper normal limits of TID ratios for different sets of acquisition-gender-stress modality-software programs.

Key words: Transient ischemic dilation; Myocardial perfusion imaging; Attenuation correction; SPECT-CT

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INTRODUCTION

Myocardial perfusion scintigraphy (MPS) is the only widely available method of assessing myocardial perfusion directly. It therefore has a clear role in the diagnosis of coronary heart disease (CHD) in patients presenting with chest pain [1]. Approximately 761 per million of population (pmp) single photon emission computed tomography-myocardial perfusion imaging (SPECT-MPI) studies are performed yearly in Europe [2]. Achievements in the instrumentation and image processing have lead to increased validation of SPECT-MPI, with overall sensitivity and specificity reaching 91 % and 87 % respectively [3]. Despite all the advances, the specificity of cardiac SPECT perfusion imaging is significantly affected by internal photon absorption [4]. Soft tissue attenuation, Compton scatter, and depth-dependent reduction of spatial resolution degrade myocardial perfusion SPECT image quality, thereby decreasing test sensitivity in the detection of coronary artery disease (CAD). In addition, localized soft tissue attenuation by the breasts, lateral chest wall, abdomen, and left hemi-diaphragm may create artifacts that mimic true perfusion abnormalities and thereby decrease test specificity [5]. Different attenuation correction (AC) techniques have been developed to overcome degradation of image quality by extra-cardiac photon attenuation. While attenuation correction can be performed using gamma-emitting external line sources, which has been shown to improve the diagnostic accuracy of SPECT imaging [6], the attenuation correction maps that are generated by these systems tend to have low count statistics and relatively low resolution and therefore lead to the use of computed tomography (CT) for attenuation correction [7]. In CT-based AC, x-ray is used to calculate transmitted fraction and attenuation coefficients. Spatial distribution of attenuation coefficients (attenuation map) is then used to obtain initial intensity of emitted photons. One important non-perfusion parameter of SPECT-MPI is transient ischemic dilation (TID) ratio which is the ratio of the stress left ventricular (LV) volumes to the rest LV volumes. TID is a clinically useful marker that is sensitive and highly specific for detection of severe and extensive CAD [8]. It has also shown to be of prognostic importance [9]. In patients with otherwise normal MPS, TID is an independent and incremental prognostic marker of total cardiac events even after significant clinical variables—age, typical angina, and diabetes—are accounted for[10]. TID can be calculated visually or more accurately by applying automatic software packages. Different thresholds for the abnormal TID ratios have been proposed according to the gender, imaging protocol and stress modalities. In the present study, we calculated and compared TID ratios for CT-AC and non-attenuation correction (NAC) acquisitions for different sets of stress modalities and software packages in the low pre-test probability group. We also evaluated the impact of gender and software programs on the calculated TID ratios. Result of this study provides information about the need to redefine abnormal thresholds of the TID ratio in the AC acquisition.

METHODS

Study Population

Our low pre-test probability group consisted of 149 patients (106 women and 43 men) with a mean age of 47.95 ± 9.18 years and mean Body Mass Index (BMI) of 29.93 ± 6.00 gr/cm^2. Patients were referred to nuclear medicine department of Shariati Hospital for myocardial perfusion imaging. Among them 84 patients (56.4 %) underwent treadmill exercise and 65 patients (43.6 %) had dipyridamole infusion as stress modalities. Diamond and Forrester method to estimate likelihood of CAD [11] was used to select patients in the low group (i.e. pre-test probability of CAD < 5 %). In this method, combination of patient's age, sex and symptoms are used for a conditional-probability analysis. None of the patients were diabetics and 6-month follow up revealed no symptoms, signs or non-invasive tests indicative of myocardial ischemia.

SPECT and SPECT-CT MPI

All patients underwent 2-day stress-rest Tc-99m sestamibi protocol. During the treadmill exercise (Bruce protocol), 740-1110 MBq (adjusted for body weight) of the radiotracer was injected at the peak exercise and the exercise was terminated 2 minutes after tracer injection. For the dipyridamole infusion, 0.56mg/kg dipyridamole was infused intravenously over 4 minutes and 740-1110 MBq of the radiotracer was injected 3-5 minutes later. Imaging was performed 15 minutes following exercise and 1 hour following dipyridamole infusion. Rest phase was performed the next day, 1 hour after injection of 740-1110 MBq of Tc-99m sestamibi. Patients fasted for at least 4 hours before stress and rest phases. For the exercise stress, patients were ordered to discontinue Ca-channel blockers and β-blockers 48-72 hours and long-acting nitrates 12 hours prior to exercise. For the dipyridamole stress, they were asked to discontinue aminophylline 36 hours and caffeine 24 hours before vasodilator stress. All patients imaged with a rotating dual-head gamma camera (Symbia T2, Siemens, Erlangen, Germany) for both the stress and rest phases. Two heads were placed in an L-Shaped configuarion. AC and NAC acquisitions were performed for each phase. Images were acquired with

a low-energy high-resolution collimator, using a 180-degree non-circular orbit from 45-degree right anterior oblique to 45-degree left posterior oblique in the step and shoot mode (32 projections, 25 seconds per projection), 20 % symmetric energy window centered at 140 keV and gating at 8 frames/ cardiac cycle. Images were stored in 64×64 matrices in the computer. For the CT acquisition, tube current of 13 mA and tube voltage of 130 kV were used. All patients were placed in the supine position with arms over their heads. CT acquisition was obtained first while the patient was asked to breathe normally. NAC images were processed with filtered back projection (FBP) algorithm, using Butterworth filter with a cut off frequency of 0.45 and order of 10. AC images were processed using Iterative Reconstruction (Flash 3D, Siemens) algorithm, using 6 iterations and 4 subsets. For the quantification of data, Quantitative Perfusion SPECT-Quantitative Gated SPECT (QPS-QGS) (Cedars Sinai, Los Angeles, California) and 4DM-SPECT (INVIA, Ann Arbor, Michigan) software programs were used for both AC and NAC methods. Two expert nuclear medicine physicians interpreted scans independently and according to 20-segment model, without knowledge of patients' clinical and ECG data. Interpretation of scans was based on the expert's subjective opinion and evaluation of suspicious artifactual defects was based on combination of visual findings, semi-quantitative perfusion scores and regional wall motion and thickening.

TID Measurements

TID ratios in both AC and NAC acquisitions were calculated using commercially available automated programs, QPS and 4DM-SPECT software. These algorithms calculate endocardial volumes (bounded by endocardial surfaces and valve planes). TID ratios are then measured by dividing stress mean LV volumes by rest mean LV volumes. Since gating acquisitions were performed only for the stress phases of the studies, non-gated stress and rest volumes were applied for TID calculations.

Statistical Analysis

Statistical analyses were performed with SPSS software (version 17, SPSS Inc.). McNemar test was used for comparison of the normalcy rates in AC and NAC methods. TID ratios were compared by paired samples t-test and independent samples t-test. P-values less than 0.05 were considered statistically significant.

Table1: Mean, standard deviation (SD) and P-value of difference between mean TID ratios calculated for 106 women and 43 men in the exercise/ dipyridamole stress modalities, with different acquisition software programs.

Software Program-Stress Type-Acquisition	Gender	Mean ± SD	P-value
QPS-Exercise-AC	Men	0.93 ± 0.13	0.016
	Women	0.86 ± 0.16	
QPS-Exercise-NAC	Men	0.91 ± 0.12	0.092
	Women	0.86 ± 0.15	
4DMSPECT-Exercise-AC	Men	0.95 ± 0.13	0.038
	Women	0.86 ± 0.22	
4DMSPECT-Exercise-NAC	Men	0.94 ± 0.17	0.029
	Women	0.84 ± 0.19	
QPS-Dipyridamole-AC	Men	0.95 ± 0.13	0.860
	Women	0.96 ± 0.14	
QPS-Dipyridamole-NAC	Men	0.93 ± 0.09	0.250
	Women	0.97 ± 0.15	
4DMSPECT-Dipyridamole-AC	Men	0.96 ± 0.09	0.860
	Women	0.97 ± 0.22	
4DMSPECT-Dipyridamole-NAC	Men	1.01 ± 0.06	0.920
	Women	1.00 ± 0.21	

*Independent samples t-test; QPS: Quantitative perfusion SPECT, AC: Attenuation correction, NAC: Non-attenuation correction

Table 2: Mean ± standard deviation and upper normal limits of TID for different sets of software-stress type-acquisition in the low pre-test probability group (106 women and 43 men).

Software Program-Stress Type-Acquisition	Gender	Mean ± SD	Upper normal limit
QPS-Exercise-AC	Men	0.93 ± 0.13	1.19
	Women	0.86 ± 0.16	1.18
QPS-Exercise-NAC	All	0.88 ± 0.14	1.16
4DMSPECT-Exercise-AC	Men	0.95 ± 0.13	1.21
	Women	0.86 ± 0.22	1.30
4DMSPECT-Exercise-NAC	Men	0.94 ± 0.17	1.28
	Women	0.84 ± 0.19	1.22
QPS-Dipyridamole-AC	All	0.96 ± 0.14	1.24
QPS-Dipyridamole-NAC	All	0.97 ± 0.15	1.27
4DMSPECT-Dipyridamole-AC	All	0.97 ± 0.21	1.39
4DMSPECT-Dipyridamole-NAC	All	1.00 ± 0.20	1.40

QPS: Quantitative perfusion SPECT; AC: Attenuation correction; NAC: Non-attenuation correction

RESULTS

Based on visual interpretation, in AC acquisition 127 patients had normal perfusion scans (normalcy rate= 85.2 %). In NAC acquisition 85 patients had normal perfusion scans (normalcy rate= 57/0%). McNemar test showed that difference between the normalcy rates was statistically significant (P <0.0001). Kolmogorov-Smirnov test revealed normal distribution of TID variable. To evaluate gender difference in the TID ratios, we performed independent samples t-test separately for each set of stress modality-acquisition-software program. For the exercise stress, mean TID ratios were significantly higher in men for all sets of acquisition-software programs with the exception of NAC-QPS in which the higher TID ratio for men was not statistically significant. For the dipyridamole stress, no significant difference was noted between men and women for all sets of acquisition-software program. (Table 1 shows the mean, standard deviation (SD) and P-values of difference for each set). TID ratios were also compared for each method (AC versus NAC) for both exercise and dipyridamole stress modalities and QPS and 4DM-SPECT software programs. Using QPS software program, paired samples t-test revealed no statistically significant difference in the mean TID ratios between the AC and NAC acquisitions for exercise stress (0.89 and 0.88 respectively, P=0.76). There was no difference in mean TID values between AC and NAC methods for dipyridamole stress either (0.96 and 0.97 respectively, P=0.81). Using 4DM-SPECT software program, no difference was noted in the mean TID ratios between AC and NAC acquisitions for the exercise (0.89, 0.88, respectively, P=0.50) or dipyridamole (0.97, 1.00, respectively, P=0.19) stress modalities. Table 2 shows the mean, SD and upper normal limits (mean + 2 SD) of TID in different sets of acquisition-stress modality-software program. In cases of gender differences in the mean TID ratios (revealed by independent samples t-test), the upper normal limits were calculated separately for each gender. Paired Samples T-Tests revealed no statistically significant difference in the mean TID ratios between the QPS and 4DM-SPECT software programs for different sets of acquisition (AC and NAC) and stress modality (exercise and dipyridamole). LV volumes were also compared between men and women by independent samples t-test which revealed significantly higher gated and non-gated LV volumes for men, with all P-values less than 0.0001 (Table 3).

DISCUSSION

The main purpose of the present study was to compare the upper normal limits of TID ratios between the AC and NAC acquisitions in the low pre-test probability group. We also compared the normalcy rates of these two methods.

Table3: Mean un-gated volumes, End diastolic volume (EDV) and End systolic volume (ESV) in the low-pretest probability group, calculated separately for 106 women and 43 men. All volumes are in milliliter (ml) and expressed as mean ± standard deviation. P-values of difference for all variables are less than 0.0001.

Variable	Men	Women
Mean rest volume (AC)	63.56 ± 13.31	41.48 ± 12.69
Mean stress volume (AC)	59.14 ± 12.46	37.76 ± 13.08
Mean rest volume (NAC)	64.26 ± 13.64	41.15 ± 13.04
Mean stress volume (NAC)	58.44 ± 12.45	37.78 ± 13.21
EDV	90.69 ± 18.10	62.35 ± 17.59
ESV	40.00 ± 12.13	21.40 ± 10.13

AC: Attenuation correction, NAC: Non-attenuation correction

Considering the normalcy rates, the study revealed a statistically significant superiority of the AC method. In the study by Corbett et al. in 195 obese patients (BMI > 30), AC was superior to NAC in terms of normalcy rate, sensitivity and accuracy [12]. In our study, obesity was not an inclusion criterion and patients with different BMIs (mean BMI of 29.93) entered the study. Diaphragmatic attenuation with resultant artifactual perfusion defects especially in the inferior and inferoseptal walls may make obese patients good candidates for the AC method. However, our results showed that all patients, regardless of their BMIs, may benefit from AC acquisition. In fact, by choosing perfusion positron emission tomography (PET) with ^{13}N-ammonia as the reference method, Fricke et al. showed that x-ray– derived AC lead to SPECT images that represent myocardial perfusion more accurately than non attenuation–corrected SPECT images. The benefit of the AC was seen primarily in the inferior wall [13]. Therefore, in this context, true perfusion defects are better delineated.

As the moderately sensitive and highly specific marker of CAD, elevated TID ratio measured by SPECT may reflect true LV cavity dilation, usually implying extensive stress-induced stunning of the left ventricle. This finding may also be secondary to extensive subendocardial ischemia, with apparent cavity dilation due to lack of visualization of the subendocardial layer of the myocardium. A combination of the two mechanisms is also possible [14]. Therefore finding the upper normal limits of TID ratios is quite important. Not much research has been done comparing the TID ratios between the AC and NAC acquisitions. In one study by Brodov et al. 96 patients with known or suspected CAD underwent dual-isotope thallium-201 rest and technetium-99m sestamibi stress SPECT MPI with CT-based AC. They found no statistical difference in the mean exercise TID ratios between NAC and AC studies (1.27 vs 1.31, respectively, P = 0.10). There was no statistical difference in the mean dipyridamole TID ratios between NAC and AC studies either (1.20 vs 1.17, respectively, P = 0.10) [15]. Our study also showed no statistically significant difference in the mean TID ratios between AC and NAC acquisitions for different sets of stress modalities and software programs. Rivero et al. evaluated the upper normal limits of TID ratio in 75 patients (33 women and 42 men) with less than 5% pre-test probability of CAD who underwent low-dose rest/high-dose exercise stress Tc-99m sestamibi MPI. They used simultaneous emission/transmission acquisition method that uses a scanning gadolinium-153 line source as the transmission source and Emory Cardiac Toolbox (ECTb; Syntermed, Inc, Atlanta, Ga) as the quantitative software**.** In their study AC processing did not change the TID index significantly whether the genders were combined or separated. They also found that female patients showed higher mean TID indices than male patients in both AC (1.01 ± 0.15 vs 0.95 ± 0.12) and non-AC studies (1.00 ± 0.15 vs. 0.97 ± 0.10), with the difference being statistically significant only in AC studies [16]. Rivero and his colleagues only compared TID ratios in the one day low-dose rest/ high-dose exercise protocol and as they proposed the elevated TID ratio in women could have a technical etiology with a combination of lower LV volumes in women and accentuated photon scatter by application of smoother filter for processing of low-dose rest studies. We used two day stress-rest protocol with the same injected dose for each phase and the same cut-off frequency for processing of the stress and rest studies. Although gated and un-gated LV volumes were all significantly smaller in women, we did not find any difference in TID ratios in dipyridamole stress and TID ratios were higher for men in the treadmill exercise. It seems that although lower LV volumes in women may result in accentuation of scatter effect in TID calculation, the

more smoothing of low-dose rest phase by application of lower cut-off frequency filters maybe responsible for the observed higher TID ratios in women in Rivero et al. study compared to the same radiotracer dose and cut-off frequency in our two-day stress-rest protocol. In another study, Kakhki et al. performed a two-day dipyridamole Tc-99m sestamibi non-gated study. They found higher mean TID ratios for 222 women with normal MPS studies as compared to 102 men with normal MPS studies(0.97 and 0.93 respectively, p=0.04). They also emphasized the possibility of technical bias similar to those proposed by Rivero to be responsible for this difference [17]. Our different results cannot be explained by the same technical bias hypothesis and further studies with more low-pretest probability population may finally lead to a general conclusion. Until then, we propose that upper normal limits shown in Table 2, be used for each set of gender-software program -stress modality- acquisition.

CONCLUSION

According to our results, AC acquisition leads to a statistically significant improvement in the normalcy rate. For the AC and NAC acquisitions, we recommend our calculated upper normal limits for TID ratios be used for different sets of genders-stress modalities-software programs.

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