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Correlation Of Coronary Stenosis Severity By 128-Slice CT Angiography To The Hemodynamic Significance Of Coronary Artery Disease By Myocardial Perfusion SPECT

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Abstract
The role of CTA in the early detection of coronary artery disease is becoming an established method. SPECT myocardial perfusion imaging is a well known established modality for assessment of hemodynamic significance of coronary stenosis. **The Aim** of current study is to determine the relation of coronary stenosis severity by CTA to the hemodynamic significance of ^{99m}Tc- tetrofosmin SPECT MPI.
Material and Methods: 72 patients with multiple high risk factors for CAD, yet with negative history and no ECG signs of coronary artery disease were included. They all underwent 128-slice CT coronary angiography. 28 patients showed abnormal lesions by CT angiography and were referred for myocardial perfusion imaging SPECT by ^{99m}Tc- tetrofosmin. The type of the stress was exercise in 10 and adenosine pharmacological in 18 cases. Interpretation of the SPECT was done both visually and by using Semi-quantitative Bull's eye model to assess for the presence / extent of myocardial ischemia.

Results: CTA showed no significant lesions (stenosis was < 50%) in 44 patients, while 28 patients showed abnormal findings. The abnormal CT findings were subdivided into equivocal results (stenosis ≥50 till ≤70%) that were present in 9 cases and 19 cases showed a significant degree of stenosis >70%. The ^{99m}Tc-Myoview MPI SPECT showed reversible defects in 4 (44%) cases only from the 9 equivocal patients. The prevalence of reversible ischemia by SPECT reaches 84% (16/19) in the 19 cases who showed >70% stenosis by CT angiography. The relation between the presence of significant coronary artery disease (>70%) and the presence of perfusion defects in SPECT was strong ($P < 0.05$). The overall positive predictive value (PPV) for CTA when taking all lesions >50% to show

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significant reversible ischemia by MPI SPECT was only 71%. However, the CTA PPV in relation to SPECT rises to 84% when considering stenosis >70%.
Conclusions: The CTA alone has limited discriminator ability for the functional significance of myocardial ischemia and the addition of MPI SPECT for all cases with stenosis >50% is recommended for proper management prior to discharge or invasive procedures.
Key Wards: CT-coronary angiography, SPECT myocardial perfusion, Coronary Stenosis.

Introduction

Coronary artery disease is a leading cause of morbidity and mortality. Multiple imaging modalities are used to screen for significant coronary artery disease. Appropriate diagnosis and therapy of coronary artery disease (CAD) frequently require information about both the functional and morphological status of the coronary artery tree.

Stress myocardial perfusion imaging (MPI) using SPECT is an established method for assessment of the functional significance of coronary stenosis and delivers valuable information for risk stratifications. Patients with stable angina and normal MPI findings have a low risk for cardiac events; therefore, coronary intervention may not be required for these patients [1-3].

Quantitative intravascular ultrasound (IVUS) indices can be reliably used for identifying significant epicardial coronary stenosis[4,5]. Myocardial fractional flow reserve appears to be a useful index of the functional stenosis severity in patients with moderate-severity coronary stenosis[6,7]. However, these modalities are invasive and relatively expensive procedures that should be avoided in low- or moderate-risk patients with a good natural prognosis.

The introduction of multidetector CT Angiography (CTA) has greatly improved the image quality of coronary arteries. The 64-slice CTA allows more precise evaluation of coronary stenosis with accurate plaque and lumen area measurements[8-11]. The calculated luminal narrowing by 64-slice CTA is well correlated with intravascular ultrasound [12]. Dual-source 64-CT with two X-ray tubes and two detector arrays mounted in the same gantry making it 128-Slice CT has recently become available [13]. In this CT machine, the two tubes emit X-ray spectra of different energy levels which will be simultaneously registered in their corresponding detector array. This gives synchronous dual-energy image data for the entire anatomy within the volume examined[14,15]. The usefulness of implementing dual tube/dual detector technique for performing contrast enhanced ECG-gated CT angiography for non-invasive coronary artery stenosis detection has recently been demonstrated [16-18].

The aim of the current work is to find the concordance between 128-slice technique CTA and ^{99m}Tc- tetrofosmin SPECT in detecting CAD. Secondly, to evaluate the ischemic functional significance of the coronary artery stenosis when seen by CTA.

Material and Methods Patients

The study was conducted prospectively, enrolling 72 consecutive patients who were referred to undergo CTA at radiology department at Saad Specialist Hospital, Al-Khobar, Saudi Arabia. Reasons for patient's referral were the presence of two or more risk factors for Coronary artery disease (CAD), typical or atypical chest pain, pathological treadmill test and shortness of breath or dyspnea. They all underwent 128-slice CTA followed by ^{99m}Tc- tetrofosmin SPECT within 1 month in a selected group of 28 patients. Patients were excluded from the study if they had cardiac arrhythmia, impaired renal function, known intolerance of iodinated contrast medium or coronary interventions between the two examinations.

Computed Tomography Procedures

All patients were examined using a dual-source CT system making it 128-slice CT (Definition, Siemens, Forchheim, Germany) in dual-energy mode. One tube of the dual-source CT system was operated with 160 mAs/rot at 140 kV, the second tube with 155 mAs/rot at 80 kV for thin (≤80 Kg) individuals and 170 mAs/rot at 100 kV for average (≤95 Kg) and larger patients. Data were acquired in a cranio-caudal direction with simultaneous recording of the patient's ECG signal. Oral propranol or atenolol (50 mg) to control heart rate was used in cases where the HR > 65. After two localization scans, a low-dose native scan of the heart was performed for coronary calcium detection and scoring. Test bolus tracking with 15 ml of non-ionic contrast agent (Ultravist® 370 mg/ml, Schering AG, Berlin, Germany) was applied to calculate the exact arrival time of contrast agent in the coronary arteries, with a region of interest in the proximal part of the ascending aorta. A bolus of 70–100 ml of contrast agent was continuously injected into an antecubital vein (50–80 ml at 5.0 ml/s, then 20 ml at 3.5 ml/s) followed by a saline chaser bolus of 50 ml at a flow rate of 3.5 ml/s. Thereafter scanning was initiated, covering the distance from the tracheal bifurcation to the diaphragmatic side of the heart during a single inspiratory breath hold for an acquisition time of 5–7 s.

All images were reconstructed with an effective slice thickness of 0.625 mm at an increment of 0.625 mm. The CTA datasets were analyzed using axial source images, multiplanar reformations (MPR) and maximum intensity projections (MIP). Coronary arteries were assessed qualitatively to evaluate flow of contrast and the diameter of the arteries. Stenoses were quantitatively assessed by obtaining the average diameter from two orthogonal MIP-reconstructed image planes to calculate the cross-sectional area. A cut-off of (a) 50% diameter stenosis [10,19-21] and (b) 70% stenosis was used for classification of significant coronary stenoses and comparison with the SPECT-MPI results.

SPECT-Myocardial perfusion imaging

The referred 28 patients underwent a 1-day Gated rest/stress MPI protocol with Adenosine pharmacological stress. A dose of 8-10 mCi of ^{99m}Tc- tetrofosmin for the resting part was injected followed 3 hours later by a second injection of 24-30 mCi of ^{99m}Tc- tetrofosmin for the stress part. Pharmacological stress test was performed with a 6-min infusion of adenosine at a standard rate of 140μg/kg/min and the stress dose of ^{99m}Tc-tetrofosmin was injected at 3 minutes of the infusion. Patients were told to withhold caffeine-containing beverages for at least 24 h, nitrates for 24 h, and beta-blockers for 48 h before the Gated SPECT study. The camera used for acquisition is a dual-head detector system (Siemens, E-Cam, Germany) equipped with a high-resolution low energy collimator. The parameters of acquisition were; a 20% symmetric window at 140 keV; a 64×64 matrix; an iso-contour orbit with step-and-shoot acquisition at 3° intervals over 180°; and a 20-s projection time per stop. Acquisitions were gated at 8 frames per R-R cycle with a 60% window of beat acceptance. The MPI SPECT images were reconstructed using filtered back-projection and the images were displayed into short axis, vertical long axis and horizontal long axis slices encompassing the entire left ventricle. In addition, polar maps of perfusion, wall motion and wall thickening were produced using a commercially available software package (Cedars QGS/QPS; Cedars-Sinai Medical Center, Los Angeles, CA, USA), yielding semi-quantitative perfusion scores at rest (SRS, summed rest score) and after stress (SSS, summed stress score). The summed difference score (SDS) was calculated as the difference of the previous two and used as an indicator of reversible perfusion abnormalities.

Two experienced nuclear medicine physicians analyzed the MPI-SPECT images reaching a consensus. Image interpretation was visually performed on short axis, horizontal long axis and vertical long axis slices, and semi-quantitative polar maps of perfusion. Defects in the anterior and septal wall were allocated to the left anterior descending coronary artery (LAD), defects in the lateral wall to the left circumflex coronary artery (LCX) and inferior defects to the right coronary artery (RCA). In the watershed regions, allocation was determined according to the main extension of the defect onto the lateral, anterior or inferior wall. Reversible perfusion defects were considered myocardial ischemia.

Statistical Methods

Prevalence of data and frequency were expressed as percentages. Quantitative data are expressed as mean ± SD. Quantitative values were compared using the two-sided Student's t test. Qualitative data are given in proportions and are compared using the chi-squared test. A p value <0.05 was considered statistically significant. Positive predictive value (PPV) and Negative predictive value (NPV) for the CT to detect functional significance of the stenosis were calculated in relation to the SPECT data. Accuracy was determined as the percentage of correct diagnoses in the entire sample.

Results

Patient Characteristics

The mean age for the 72 patients of this study population was 55 ± 12 years. The prevalence of male patients included was higher 42 (58%) compared to 30 (42%) females. Based on clinical assessment and the presence of risk factors for CAD, the pretest likelihood of CAD were low, intermediate, and high in 25 (34.7%), 36 (50%), and 11 (15.3%) patients, respectively.

CTA findings:

Image quality was very good to excellent in 58 patients (80.5%), adequate in 11patients (15 %), heavily calcified in 3 patients (4%).

On patient basis, 44 patients (61%) were classified as having no significant coronary artery lesions which were supported semi-quantitatively as having no stenosis or, if any then less than 50%. The remaining 28 patients included in this work showed abnormal coronary artery findings by CT criteria. The findings in these 28 patients were subdivided to 19 cases who have definite CAD lesions where the stenoses are > 70% and 9 cases showed equivocal findings where the stenosis degrees were non-obstructive and varies between ≥50 till ≤70%. These 28 cases were referred to nuclear medicine for MPI imaging by ^{99m}Tc-tetrofosmin SPECT.

^{99m}Tc-tetrofosmin Myocardial Perfusion SPECT:

^{99m}Tc-tetrofosmin GATED-SPECT was successfully performed in all 28 patients and all image data sets were adequate for image interpretation. Visual image analysis revealed perfusion abnormalities in 20/28 patients (71.4%). These 20 patients were the sum of 4 from the 9 patients with equivocal CTA findings and 16 out of the 19 patients with definite CTA findings of coronary artery stenosis.

The number of coronary arteries and their related territories evaluated by GATED-SPECT were 84. Table 1 showed the MPI findings. The Gated SPECT detected 24 reversible and 6 fixed perfusion defects, indicating functionally relevant stenosis in 30 of 84 coronary arteries. Of the 24 reversible perfusion defects 14 (58%) were located in the LAD territory, 4 in LCX and 6 in RCA territories. For the fixed defects, 3 were in RCA territory, 2 in LAD and 1 in LCX territories. The overall semi-quantitative perfusion scores (SSS, SRS, SDS) were significantly higher in the 20 positive patients compared to the negative MPI patients (SSS 7.0 ± 6.5 Vs. 2.1 ± 3.0 ($p < 0.001$), SRS 3.7 ± 5.4 Vs. 0.7 ± 1.6 ($p = 0.008$) and SDS 5.3 ± 3.7 Vs. 1.7 ± 2.1 ($p < 0.001$). The Summed Difference Score (SDS) that signifies reversibility was elevated in patients with reversible perfusion defects compared to those with fixed perfusion defects (6.0 ± 3.3 Vs. 1.2 ± 1.8 ($p < 0.001$).

Stenosis Severity by CTA in relation to GATED SPECT Perfusion Data

The Gated SPECT showed perfusion defects in 16 out of the 19 patients who had >70% coronary stenosis by CTA denoting concordance in 84% (**figure 1**), while in three patients the GATED SPECT was negative for hemodyanmically significant ischemic heart disease (non-concordance of 16%) (table 2 and **figure 2**). The number of perfusion defects was 25, four patients had 2 reversible perfusion defects each, 3 had a combination of reversible and fixed defects each (8 defects). The 9 rest patients had only single reversible zone each with no fixed defects (Table 2).

For the subset of patients (n=9) who had equivocal findings of coronary stenosis around 50%, the prevalence of perfusion defects by GATED SPECT was low and present in 4 patients only (44%). One patient had one reversible ischemic and one fixed defect, and the other three had single reversible ischemic zone each. The overall positive predictive value (PPV) for CTA for lesions between 50 and 70% was 44%, and was 71% when taking all lesions ≥50% to show significant reversible ischemia by MPI SPECT. However, the CTA PPV in relation to SPECT rises to 84% when considering stenosis >70%.

Discussion

Since its introduction, multi-slice CT angiography has been playing an increasing role in the diagnosis of coronary artery stenosis. Systematic reviews performed to detect its diagnostic value returned sensitivity and specificity of 92% and negative predictive value of 98% in vessel-based assessment compared to conventional coronary angiography [22]. However, the presence of coronary artery disease does not always mean functionally relevant stenosis, and even in angiographically confirmed coronary stenosis, normal myocardial perfusion scintigraphy can be present and generally signifies a low risk (1%) of cardiac events [23].

Coronary CTA Findings

In the current work, the CT showed that only 28 patients (39%) showed abnormal stenotic lesions by CT while 44 patients were free from coronary artery stenosis by CT criteria. This goes similar to the findings of other literature [24-27] in the group of patients with low to intermediate probality for CAD.

Thilo et al. [26], found that only 6/24 patients (25%) had a Stenosis ≥ 50% at CTA. In another work on 100 patients [27] 70 patients (70%) had abnormal multi-slice CT coronary angiography, however only 24 patients (24%) had a significant, ≥ 50% stenosis. Sato et al [28], on their study on 104 patients define coronary artery stenosis as luminal narrowing ≥ 60% and they reported that 71/104 patients (68%) showed Coronary artery disease. On a vessel basis, only 105 (37%) of 285 evaluable coronary arteries were identified to have coronary artery disease while 180 (63%) coronary arteries were normal with no significant stenosis.

CTA in correlation to SPECT findings

Our study showed that CTA has a modest ability to predict the functional relevance of coronary lesion in the range of 50-70% stenosis (PPV 44% for lesions between 50% and 70%, and 71% considering all patients with lesions >50%). This confirms previous studies with similar results. Schuijf et al. [29] reported that 20 out of 40 patients with obstructive coronary artery disease (i.e. at least one >50% stenosis) on CTA have perfusion defects on myocardial perfusion imaging (50% PPV). Similarly, Hacker et al. reported PPV of 32% (vessel-based analysis) and 60% (patient-based analysis) for lesions >50% [24]. In two separate studies, Gaemperli et al. reported a 50% and 58% PPV for CTA in detecting myocardial perfusion defects considering lesions >50% [25,30]. For stenosis between 60% and 70%, Sato et al. reported perfusion defects in 9 out of 27 vessels (33% PPV). This value increased to 55% when adding all vessels with stenoses >60% [28]. Most recently, Nicol et al. stated a 50% PPV for CTA lesions ≥ 50% in detecting myocardial perfusion defects [31]. As noticed, most of these studies report a PPV around 50%, confirming that using the widely accepted value for significance regarding coronary artery stenosis is not good enough in predicting its functional relevance. When we used 70% stenosis as our lower limit, only 3 out of 19 patients showed normal myocardial perfusion scintigraphy, giving a PPV of 86%. Although, Sato et al., [28] reported a PPV for 70% lesions lower than our current work (only 66%), however, when they used 80% stenotic lesions a higher

PPV of 86% was found in their work. Similar lower PPV (68.2%) was reported by Gaemperli et al. for 75% stenotic lesions (15 out of 22 patients showing perfusion defects on myocardial perfusion study) [30].

The current work discussed the diagnostic use of CTA in correlation to the MPI findings in patients with low to intermediate likelihood of CAD, yet the full prognostic potential of CTA was not addressed. It is anticipated that coronary CTA will have strong prognostic power since the severity of CAD by selective conventional angiography have been known to predict outcome in subgroup of patients that will likely benefit from revascularization [32]. Nevertheless, the ability of conventional coronary angiography to predict outcome of revascularization in randomized trials was dependent on the severity of inducible ischemia [33,34]. Berman et al., [34,35] consider that in a large proportion of patients with coronary lesions on CTA, further assessment of the extent and severity of ischemia by SPECT- MPI will effectively identify patients who will have a survival benefit from coronary revascularization.

In conclusion; Coronary artery CTA alone has limited discriminator ability for the functional significance of inducible myocardial ischemia. Both CTA and stress MPI provide complementary information for the clinical evaluation of coronary lesions. Accordingly, the addition of MPI SPECT for all cases with stenosis ≥50% is recommended for proper management prior to discharge or invasive procedures.

Table 1: Myocardial perfusion SPECT findings in the evaluated Patients.

Coronaries evaluated	Total Number	3 x 28=84	**P values**
Defects			
	Reversible	24	
	Fixed	6	
LAD territory			
	Reversible	14	
	Fixed	2	
LCX territory			
	Reversible	4	
	Fixed	1	
RCA territory			
	Reversible	6	
	Fixed	3	
Summed Stress Score (SSS)			
	Positive SPECT	7.0 ± 6.5	<0.001
	Negative SPECT	2.1 ± 3.0	
Summed Rest Score (SRS)			
	Positive SPECT	3.7 ± 5.4	=0.008
	Negative SPECT	0.7 ± 1.6	
Summed Difference Score (SDS)			
	Positive SPECT	5.3 ± 3.7	< 0.001
	Negative SPECT	1.7 ± 2.1	

Table 2: Correlation between CTA degree of coronary stenosis and the perfusion defects seen by SPECT perfusion images

		Patients (n)	**Stenosis**	**Stenosis**
			≥50 - <70%.	> 70%.
SPECT +ve		20	4	16
SPECT -Ve		8	5	3
Perfusion Defects				25
	Reversible only	13		17
	Fixed only	**		**
	Reversible and Fixed	3		8
Perfusion Defects			5	
	Reversible only	3	3	
	Fixed only	**	**	
	Reversible and Fixed	1	2	

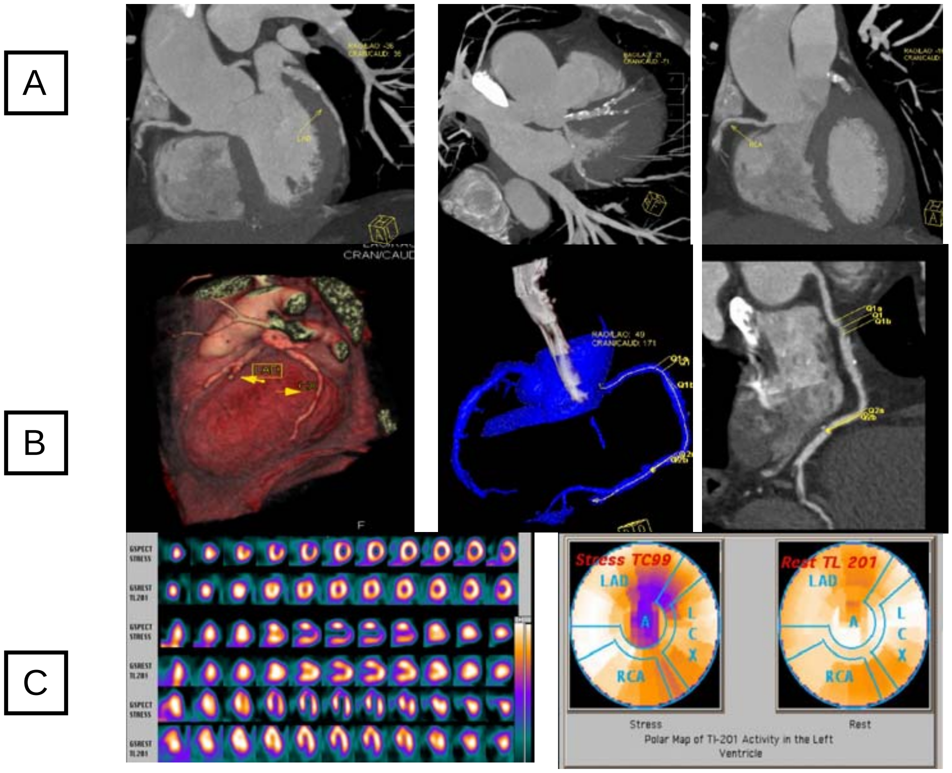

Figure 1: Male patient 55 years old, the CTA (Row A) showed significant disease in LAD with heavy calcification (90%) and in LCX artery (70%) and mild disease in RCA (60%). Row B showed the 3D reconstruction with prominent disease in LAD and LCx arteries and methods used for quantitation of stenosis.

Row C, SPECT perfusion study that showed significant reversible ischemia in apex, anterior and antro-lateral walls with transient ischemic dilatation denoting multivessel disease.

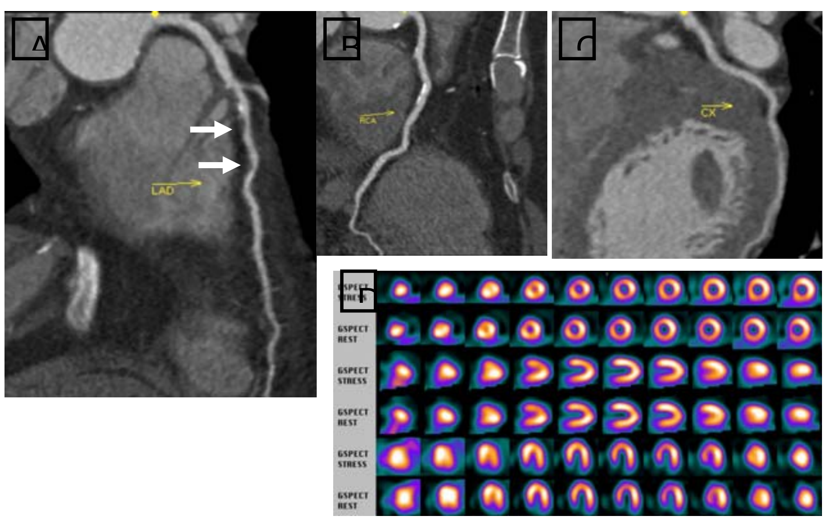

Figure 2: Male patient 60 years old with multiple risk factors for CAD. A, The CTA showed calcification and 2 areas of significant stenosis (70%) (White arrows) in the LAD. B, Mild degree of stenosis (50%) in RCA while LCx is normal as seen in C. The SPECT study D, showed normal homogenous perfusion in all myocardial walls.

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