ORIGINAL RESEARCH PAPER

Cardiology

COMPARATIVE STUDY OF COMPUTERIZED TOMOGRAPHY CORONARY ANGIOGRAPHY (CTCA) VS. TREADMILL STRESS TEST (TMT) IN PATIENTS WITH SUSPECTED CORONARY ARTERY DISEASE

KEY WORDS: Computerized tomography coronary angiography (CTCA), Treadmill Stress Test (TMT)

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ABSTRACT

Background: There are few studies that compared CTCA in patients presenting with chest pain, probably ischaemic (i.e., atypical) with negative or inconclusive TMT in outpatient department. **Objective:** To assess 64-slice CTCA findings in patients with suspected ischaemic chest pain and negative or inconclusive TMT. **Methodology:** Enrolled patients underwent TMT and classified as TMT negative or inconclusive patients. These patients underwent CTCA and findings were analysed. **Results:** 50 patients completed the study protocol. Of these, 31 (62%) were TMT negative and 19 (38%) were TMT inconclusive. CTCA showed obstructive CAD in 19 (38%) patients; 7 (36%) with negative TMT and 12 (63%) with inconclusive TMT. Overall, CTCA was more predictive of diagnosing obstructive lesion in TMT inconclusive group as compared to TMT negative group. **Conclusion:** In patients with atypical chest pain with negative or non-diagnostic TMT, CTCA provides an important diagnostic tool for rapid triaging of such patients.

INTRODUCTION:

Coronary artery disease (CAD) is leading cause of death worldwide with an enormous burden on health care systems. Annually, more than 10 million stress tests and approximately one million diagnostic cardiac catheterizations are being performed in the U.S. alone. CAD requires an accurate diagnosis and early management hence invasive coronary angiography (CAG) is considered a gold standard for the diagnosis of CAD but it is an invasive technique hence CAG with or without intravascular sonography is reserved for patients with a sufficiently high probability of disease. Considering it more invasive , more expensive test and associated high risk of morbidity. To avoid risk of invasive procedure of angiography in low to intermediate risk patients there are many non invasive methods for evaluation including the exercise treadmill test(TMT), stress echocardiography, stress myocardial perfusion scintigraphy, pharmacologic nuclear stress testing, electron beam Computed Tomography (EBCT), multi detector CT (MDCT), and stress cardiac magnetic resonance imaging.

Duke treadmill score (DTS) in TMT is one of the most effective and important non-invasive techniques of diagnosis, risk stratification and prognostic assessment of CAD. Specificity of TMT is lowered somewhat by resting ST depression of less than 1 mm, although it is still the first option in evaluation of possible CAD in such patients with an intermediate pre-test probability. Specificity is also lowered by LVH with less than 1 mm of ST depression and use of digoxin with less than 1 mm of ST depression, but the standard exercise test is still a reasonable option in such patients.

In contrast, other baseline ECG abnormalities such as pre-excitation, ventricular pacing, greater than 1 mm of ST depression at rest, and complete left bundle branch block greatly affect the diagnostic performance of the exercise test. Imaging modalities are preferred in these subsets of patients. Also, TMT has got lower diagnostic accuracy in women.In the elderly, due to the greater prevalence of CAD, it has got a slightly higher sensitivity than in younger patients with a slightly lower specificity, which may reflect the coexistence of LVH due to valvular disease and hypertension.

A MDCT technology can help us in assessment of disease presence, location, severity of coronary artery disease especially patients with negative or borderline / inconclusive TMT yet clinically symptomatic. Recent advances in CT technology allows CTCA and left ventricular (LV) functional assessment. 64-slice spiral CT allows the non-invasive angiography diagnosis of anatomic structures and pathological changes with quick movement organs such as coronary arteries and heart to become possible. DTS, CART and 64-slice spiral CT are the current research focus in the assessment of diagnostic value for CAD. CTCA can have challenging role over the default non invasive method TMT for patients presenting with non-acute chest pain.

The present study was planned in patients presenting with suspected ischaemic chest pain and negative or inconclusive TMT and compare it with their coronary anatomy by CTCA.

MATERIAL AND METHODOLOGY:

The present study is a prospectively planned analysis of 50 patients with atypical chest pain, who presented in the out-patient department of our department of cardiology.

Patients presenting as chest pain, possibly ischaemic in origin (atypical chest pain) underwent baseline evaluation followed by TMT using standard Bruce protocol. Only patients with negative or inconclusive TMT were enrolled in the study and later on, sent for CTCA.

Methods:

Enrolled patients underwent TMT and classified as TMT negative or inconclusive patients. TMT positive were excluded from the study. These patients with TMT negative and inconclusive, with high suspicion of underlying coronory artery disease underwent CTCA and findings were analysed.

INCLUSION CRITERIA:

1. Patients presenting with chest pain, possibly ischaemic in origin (atypical chest pain).
2. Patient symptoms not suggestive of acute coronary

syndrome.
3. Not a known case of CAD.
4. No prior acute coronary syndrome, prior PCI or CABG.
5. Possibly ischemic pain but TMT negative or inconclusive not responding to treatment

EXCLUSION CRITERIA:

Exclusion for TMT:

1. Patients presenting as classical angina or non cardiac chest pain.
2. Baseline ECG abnormalities such as LVH with ST depression of >1 mm, LBBB, pre-excitation, ventricular pacing, > 1mm of ST depression
3. Patients not able to perform TMT or are having contraindications for TMT.

Exclusion for MDCT:

1. patients with contraindication to intravenous contrast agents (contrast allergy)
2. elevated serum creatinine
3. Patients with rhythum abnormalities, for ex., atrial fibrillation, frequent ventricular ectopy (>10 extra systoles per minute),
4. patients who have documented CAD by prior CART or MDCT and/or patients with coronary artery stents, prior angioplasty, or prior coronary artery bypass grafts (CABG)
5. patients who have had prior cardiac imaging (within the past year) with normal result including CART, CTCA or nuclear stress testing.

BASELINE EVALUATION

(i) Detailed history and physical examination of all patients who were enrolled in the study.
(ii) Routine blood investigations e.g. Hb. TLC, DLC, blood urea, serum creatinine, serum Na+ /k+, random blood sugar
(iii) Treadmill testing using standard Bruce protocol

TREAD MILL TESTING (TMT):

The exercise ECG testing facility conformed to the American Heart association (AHA) guidelines for clinical exercise ECG testing laboratories.

All the enrolled patients then underwent TMT. TMT was done according to standard Bruce protocol.

On the basis of ECG response to exertion and symptoms, results of TMT were judged as:

1. TMT positive: >1mm ST depression below baseline or slow upsloping ST depression or ST elevation on exertion.
2. TMT inconclusive: patients who failed to achieve 6 METs or who failed to achieve 85% of age-predicted maximum heart rate without ischemic responses in ECG.
3. TMT negative: patient who completed their protocol, achieved target heart rate, without symptoms and ECG changes of ischaemia.

ECG changes with rapid upsloping changes or ST depression < 1 mm was also considered as negative.

Patients who were TMT negative or inconclusive (as per standard protocol), underwent coronary MDCT to visualize their coronary anatomy. TMT positive patients were excluded from the study and were triaged for further management.

An assessment of the correlation between coronary MDCT and TMT was done for risk stratification of such patients.

MDCT SCAN:

MDCT scans (Brilliance 64, Philips Brilliance 64, Philips Medical Systems, Cleveland, Ohio) were performed with retrospective ECG gating. An oral beta blocker (metoprolol 50 to 100 mg or atenolol 50 mg) and/or intravenous beta blocker (metoprolol 2.5 to 10 mg) (or oral calcium antagonist [verapamil 80 mg] in asthmatic patients) was used to lower heart rate. Oral beta blocker was administered when heart rate was >70 bpm, 1 hour before scanning. If heart rate was still >70 bpm on arrival to the CT suite and no medical contraindication existed, intravenous metoprolol was added

Coronary Calcium Score:

The coronary calcium score (Agatston score) was measured in a non–contrast enhanced scan. Low dose anterio- posterior scanogram of chest was taken and volume of heart was localised to do plane scanning for calcium scoring.

The calcium score is generated using software specifically designed for this purpose. Semiquantitative scores are based on a section-by-section analysis of the CT images. There are three scoring methods: the Agatston-Janowitz score, the volume score, and the mass score. The Agatston- Janowitz score was the initial method for calcium quantification and is the most widely used. To be included in the Agatston- Janowitz score, CAC must reach a threshold of 130 Hounsfield Units (HU) and cover an area of at least 1 mm2; calcifications that are lower in attenuation or smaller in size are not included in the score. The score of each calcification is calculated by multiplying the area of the CAC by an attenuation weighting factor based on the highest HU value of the CAC, a score ranging from 1 to 4. A vessel score is the sum of all CAC scores of that vessel, and the total calcium score is the total of all CAC scores from all vessels.

Computed Tomography Coronary Angiography:

A contrast enhanced scan was then performed with a bolus of 40 to 100 mL contrast medium (Ultravist 370 mg I/mL; Schering AG, Berlin, Germany) injected into an ante-cubital vein at a flow rate of 5 to 6 mL/s, followed by a 50 mL saline chaser bolus. For giving intra venous contrast bolus, either a biphasic or a triphasic technique is used.13 A biphasic technique uses saline as the second phase of the bolus, immediately after the contrast injection, to completely wash out contrast material from the right heart chambers and to eliminate streak artefacts across the deep right atrio-ventricular groove in which the right coronary artery (RCA) sits. In a triphasic bolus, contrast material is followed by a mixture of saline and contrast material, so that there is some visualization of the morphology of the right heart chamber.

Scanning was performed at 120 kV, effective tube current 600 to 1000 mA (higher mA in obese patients), slice collimation 64 x 0.625 mm acquisition, 0.4 second gantry rotation time, and pitch 0.2. Overall scan time (as well as breath hold) was usually <15 seconds. Total time for the MDCT examination was typically 10 to 15 minutes.

Retrospective ECG gating was done. Radiation dose-reduction measures were also used, including tube current modulation techniques. Typically, in patients with a fixed R-R interval, tube current modulation was used, with the mA being reduced at the phases of the R-R interval that were generally not used for viewing the coronary arteries. In patients with a normal stable sinus rhythm and a heart rate of 65 beats per minute or lower, images were acquired only at the LV end-diastole during the cardiac cycle. This technique significantly reduced the radiation dose without compromising image quality, but it sacrificed the dynamic cardiac functional data. LV end-diastole is when there is relatively little motion and the greatest coronary artery blood flow, when the coronary arteries are usually the most optimally visualized. LV end-systole is the second relatively motion-free part of the cardiac cycle and may be used when LV end-diastole is insufficient, particularly for evaluation of the vertical portions of the RCA and LCX coronary artery. Lesions with >50% stenosis were considered as obstructive and lesions with <50% stenosis were considered as non obstructive.

STATISTICAL ANALYSIS:

Statistical analysis was performed with the use of SPSS 15.0 software package and Graph Pad InStat online software. A probability value of <0.05 was considered significant for statistical testing. Demographics, traditional risk factors, clinical events, and prevalence of plaque and stenosis as detected by MDCT are presented as mean ± SD or median and interquartile range for continuous variables and as percentages for categorical variables.

Comparison of the factors between the groups was done by Chi-square test or Fischer's test. To determine the accuracy of coronary MDCT, we calculated conventional measures of diagnostic accuracy based on a binomial distribution for the absence of plaque and the absence of significant stenosis for the detection of CAD. The Chi-square test was used to compare proportions and measures of diagnostic accuracy between groups.

Results

We prospectively analysed 50 patients with atypical chest pain, suspected to be ischaemic in origin, and with negative or inconclusive TMT with MDCT. In the present study, 50 patients of atypical chest pain underwent TMT, followed by MDCT coronary angiography. Mean age of the patients was 51.74 ± 7.65 years and 22% of the patients were females (table 1).

Table 1: Baseline variables'

Variables	No. of patients (n=50)
Age (years)	51.74 ± 7.65
Female sex	11 (22%)
Hypertension	14 (28%)
Diabetes mellitus	19 (38%)

After TMT, patients were labelled as either with negative or inconclusive test. Out of 50 patients, 31 (62%) were TMT negative and 19 (38%) were TMT inconclusive. Number of patients in the two groups were not equal, as 50 consecutive patients were enrolled in the study. Despite this, baseline characteristics were similar in the two groups in terms of age, sex, and risk factors (hypertension and diabetes mellitus), but there were more percentage of patients with hypertension and diabetes mellitus in TMT inconclusive group as compared to TMT negative group (table 2).

Table 2: Baseline characteristics of TMT negative and inconclusive groups

Variables	TMT- Negat (n= 31)	TMT- inconclusive (n= 19)	Total (n=50)	p value
Age (years)	51.42± 7.38	52.26± 8.24	51.74± 7.65	0.741
Female sex	6 (19%)	5 (26%)	11 (22%)	0.727
Hypertension	7 (22%)	7 (37%)	14 (28%)	0.339
Diabetes Mellitus	10 (32%)	9 (47%)	19 (38%)	0.372

Patients with inconclusive TMT, as compared to patients with negative TMT, had poor exercise capacity (exercise time: 5:24± 1:14 v/s 7:13± 1:37 minutes, p = 0.0001) and achieved less METs (6.33± 1.67 v/s 7.86± 1.97, p= 0.007) (table 3). The difference of both these variables in the two groups were statistically significant.

Table 3: Comparison of exercise capacity and METs achieved in TMT negative and inconclusive groups

Variables	TMT- Negative (n= 31)	TMT- inconclusive (n= 19)	Total (n= 50)	p value
Exercise time (minutes)	7:13± 1:37	5:24± 1:14	6:32± 1:43	0.0001
METs	7.86± 1.97	6.33± 1.67	7.28± 1.99	0.007

Coronary artery calcium score: A total of 19 (38%) patients had obstructive CAD on MDCT. Out of these 19 patients, 7 (36%) patients were with negative TMT and 12 (63%) patients were with inconclusive TMT.

Out of 31 patients with negative TMT, 7 (22%) patients had obstructive CAD on MDCT. Similarly, out of 19 patients with inconclusive TMT, 12 (63%) patients had obstructive CAD. The difference between the two groups were statistically significant (p = 0.0067). Mean Agatston score was also higher in patients with inconclusive TMT as compared to negative TMT (83.12 v/s 51.77, p = 0.3366). (table 4)

Table 4: Comparison of mean Agatston score and obstructive CAD in both TMT groups

Variables	TMT- Negativ (n= 31)	TMT- inconclusive (n= 19)	Total (n=50)	p value
Agatston score	51.77	83.12	63.69	0.3366
Obstructive CAD	7	12	19 (38%)	0.0067

Computed Tomography Coronary Angiography: Out of 50 patients, 19 (38%) patients had obstructive CAD (≥ 50% stenosis) on MDCT, In TMT inconclusive group has total of 19 patients, 12 (63.15%) had obstructive CAD, while 7 (36.84%) had non obstructive CAD on CT coronory angiography. In TMT negative has total of 31 patients, obstructive CAD was present in 7(22.6%) while non obstructive CAD present in 24(77.4%). Among total patient with obstructive CAD (19), TMT was negative in 7 (36.8%) and inconclusive in 12 (63.2%). Similarly among non obstructive CAD (31), TMT was negative in 24 (77.4%) and inconclusive in 7 (22.6%) (table 5). The difference between the two groups were statistically significant (22% v/s 63%, p = 0.0041). So, a significantly large percentage of patients in TMT inconclusive group have had obstructive CAD.

Table 5: percentage of patients with obstructive and non obstructive CAD in CT coronory angiography in TMT negative and inconclusive group.

TMT	OBSTRUCTIVE CAD	NON OBSTRUCTIVE CAD	P value (unequal variance)
NEGATIVE (n=31)	7 (22.5 %)	24 (77.41%)	0.0041
INCONCLUSIVE (n=19)	12 (63.15%)	7 (36.84%)	
TOTAL (n=50)			

Study limitations: An important drawback of the present study was the relatively small sample size. The number of stenosis in individual segments of coronary arteries were less in number, and because of that, it was difficult to calculate diagnostic accuracy of each segment of coronary artery. However, larger studies with large population size will be required to exactly ascertain the value of MDCT in diagnosing CAD in each segment of coronary artery.

DISCUSSION:

Chest pain presenting to the outpatient department is triaged into classical angina, atypical chest pain, or non cardiac chest pain. Patients with atypical chest pain and with intermediate probability of CAD are further investigated with stress studies. TMT is the most commonly used stress study in such cases. But, TMT is misleading in some patients for its low sensitivity, i.e. in the range of 60-70%.

In study of Jinsik park on efficacy and safety of the CT coronary angiography based on approach for patient with acute chest pain{1} . Of the 296 enrolled patients, 103 (34.8%) were classified as Group I (low risk), 104 (35.1%) classified as Group II (intermediate risk), and 89 (30.0%), as Group III (significant lesion). There was little difference in the baseline characteristics between the three groups except mean age, which was significantly higher in Group III.

The Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) trial was an observational cohort study of acute chest pain patients presenting to the emergency department with normal initial troponin and a nonischemic ECG. Predictors of plaque included older age, male sex, diabetes, hypertension, hyperlipidemia, lower functional capacity, and a lower Duke Treadmill Score. Both a positive ETT and a low Duke Treadmill Score were significant univariate and multivariable predictors of stenosis >50% on CTCA Whereas the prevalence of stenosis by CTCA was greater among patients with more risk factors, coronary stenosis was not present among men <40 years old or women <50 years old or individuals who achieved at least 13 metabolic equivalents on ETT.{2}

Similarly in our study mean age of patients was 51.74 years, 22% of patients were females while 78% were males. Hypertension (37% vs 22%) and diabetes mellitus (47% vs 32%) were more prevalent in group with TMT inconclusive as compared to negative TMT

Current US stable ischemic heart disease guidelines favor noninvasive functional testing for myocardial ischemia in most patients, reserving anatomic testing using coronary computed tomography coronary angiography (CTCA) for patients without established CAD who have already undergone functional testing.{3} Numerous large-scale randomized, controlled comparative effectiveness trials, such as PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain; n = 10,003) and SCOT-HEART (Scottish Computed Tomography of the Heart; n = 4,146), have established that coronary CTCA is at least as effective as strategies that do not utilize coronary CTA for all studied cardiovascular outcomes. In fact, among randomized controlled imaging-guided trials, coronary CTCA has been consistently associated with reduced incident myocardial infarction (MI) in both acute and stable chest pain populations. In a meta-analysis of randomized trials, stable chest pain patients who underwent coronary CTCA were noted to have a 31% lower risk for MI (pooled risk ratio 0.69; 95% confidence interval, 0.49-0.98), a finding that was consistent across the 3 included trials, including PROMISE and SCOT-HEART (I-squared = 0%) These test-driven changes in post-test management related primarily to visualization of nonobstructive CAD resulted in a 50% reduction in incident MIs within fewer than 2 years of follow-up.

As per Gallagher, et al.{4} and previous studies comparing CT angiography with traditional invasive coronary angiography suggest further testing, such as stress nuclear imaging for any patient with stenosis more than 25% or CCS of greater than 100 and further recommends cardiac catheterization of any patient with greater than 70% stenosis by MSCT As per Bashir, et al.{5} prevalence of CAD in CTCA group was 14.37% and the prevalence of CAD in invasive angiography group where patients were age, sex and risk matched was 16.87%. The results in two groups were comparable with slight increased prevalence in invasive angiography group. The prevalence of diseased coronaries increased with increasing age, 0% prevalence was seen in patients <45years age compared to 33% in those>60 years of age. In CTCA group 26% patients among diseased group had non-obstructive lesions and rest 74% showed significant and severe disease. Patients with CAC>100 showed higher prevalence of significant and severe disease, the positivity rate of CAC increased with age and were more common in males. Negative calcium scores although showed less prevalence of significant disease but does not reliably exclude severe disease especially in young because of presence of non-calcified plaques leading to acute coronary syndromes.{6}

In our study 50 patients completed the study protocol as per inclusion and exclusion criteria, underwent TMT and were classified as TMT negative and TMT inconclusive. Out of 50 patients, 31 (62%) were TMT negative and 19 (38%) were TMT inconclusive. Mean age of patients were 51.74 ± 7.65 years and 22% were females, 28% were hypertensive and 38% were diabetic (table 1). Number of patients in both TMT negative and inconclusive group were not same but baseline characteristics were nearly same in both the groups, although with more co-morbidities in patients with inconclusive TMT with higher prevalence of hypertension and diabetes mellitus (table2).

Patients with inconclusive TMT had poor exercise capacity and achieved less METs (6:33±1:67 mts) as compared to patients with negative TMT (7:86± 1:97 mts) Both of these variables were statistically significant, with p value < 0.05. (table 3)

A total of 19(38%) patients had obstructive CAD on MDCT. Out of these 19 patients, 7(36%) patients were with negative TMT and 12(63%) patients were with inconclusive TMT. Out of 31 patients with negative TMT, 7(22%) patients had obstructive CAD on MDCT. Similarly, out of 19 patients with inconclusive TMT, 12(63%) patients had obstructive CAD. The difference between the two groups were statistically significant (p = 0.0067) (table 4).

Mean Agatston score was also higher in patients with inconclusive TMT

(p = 0.3366) (table 4)
A total of 31 patients were in TMT negative group with 7(22.5%) had obstructive CAD, while 24(77.41%) had non obstructive CAD. In TMT inconclusive group has total of 19 patients, 12(63.15%) had obstructive CAD, while 7(36.84%) had non obstructive CAD on CT coronory angiography, among total patient with obstructive CAD (19), TMT was negative in 7(36.8%) and inconclusive in 12(63.2%).similarly among non obstructive CAD (31), TMT was negative in 24(77.4%) and inconclusive in 7(22.6%) which was statistically significant with p value <0.05 (table 5).

CONCLUSION:

Because of the low sensitivity and all other drawbacks of TMT, negative test or inconclusive test should not be considered as normal, should be confirmed by further tests such as repeat TMT, CT coronary angiography, invasive coronory angiography, thallium scan, stress echo test. Computed tomographic coronary angiography has become a valuable tool to screen low and intermediate risk cardiac disease. Patients who test positive on CTCA should go for invasive angiography for definitive opinion.

Abbreviations-

TMT- treadmill stress test
CAD- coronary artery disease
MET- metabolic equivalent of task
EBCT- electron beam computerized tomography
MDCT- multidetector computed tomography
DTS- duke treadmill score
PCI- percutaneous coronary intervention
CABG- coronary artery bypass graft
LVH- left ventricular hypertrophy

M.I- myocardial infarction
CTCA- Computerized tomography coronary angiography
CAC SCORE- coronary artery calcium score
RCA-right coronary artery
LCX- left circumflex artery
ETT- exercise tolerance test
CCS SCORE- coronary calcium score
MSCT- multislice ct angiogram

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