VARIous Treadmill Test Parameters Predicting Normal Coronary Anatomy on Coronary Angiography
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ABSTRACT

BACKGROUND
Patients with cardiac Syndrome X defined as typical chest pain associated with electrocardiographic changes suggestive of transient myocardial ischaemia, despite normal coronary angiograms, constitutes diagnostic and therapeutic challenges. Syndrome X is not a “rare syndrome”, as up to 30% of patients undergoing diagnostic angiography for the assessment of typical chest pain are found not to have obstructive coronary artery disease. Various mechanisms were explained for inducible ischaemia in Syndrome X population. One of hypothesis that ischaemia at watershed zone of two coronary vessels is one of contributory factors for myocardial ischaemia. In this study we define various TMT parameters which predict normal coronary angiogram in TMT positive population.

MATERIALS AND METHODS
It was a prospective study of population who was positive for myocardial ischaemia in treadmill test which were taken for coronary angiography. Various TMT parameters was studies in population having normal coronary angiography and population having significant coronary artery diseases.

RESULTS
200 participants who were taken for coronary angiography based on positive myocardial ischaemia, 70 were having normal coronary angiography called Syndrome X and 130 were having significant coronary artery disease (CAD). Treadmill parameters like Duke Treadmill Score (DTS) were -2 in Syndrome X group and -11 in CAD group, Average MET at which ST / T abnormality started were 6.3 in Syndrome X group and 3.2 in CAD group, ST–HR index were 6.6 in Syndrome X and 21.2 in CAD group. Reasons for termination were nonspecific complain in 74.28% in Syndrome X group and 13.84% in CAD group. Type II LAD were present in 28.57% in Syndrome X group and 16.15% in CAD group.

CONCLUSION
We found that patients in cardiac Syndrome X group were having favourable TMT parameters like greater METS achieved, lesser DTS, ST-HR Index and appearance of ST-T wave abnormalities at grater METS or HR. Further, most of these patients were having type 2 LAD, creating LV apex as a relatively ischaemic zone.

KEYWORDS
Syndrome X, TMT, Duke Treadmill Score.


BACKGROUND
Patients with cardiac Syndrome X defined as typical chest pain associated with electrocardiographic changes suggestive of transient myocardial ischaemia despite normal coronary angiograms, continue to constitute a diagnostic and therapeutic challenges. Cardiac Syndrome X is not a “rare syndrome”, as up to 30% of patients undergoing diagnostic angiography for the assessment of typical chest pain are found not to have obstructive coronary artery disease. Cardiac Syndrome X encompasses a variety of pathogenic subgroups and is most typically seen in peri and post-menopausal women.234 Reported pathophysiological abnormalities are myocardial ischaemia, abnormal coronary blood flow,5 coronary microvascular abnormality,6 abnormal cardiac autonomic regulation,6 endothelial dysfunction,78 abnormal platelet aggregation,8 abnormal pain perception,910 metabolic12 and hormonal abnormalities, systemic vascular abnormalities. We studied the exercise TMT response of such patients and tried to differentiate it from true positive response of hemodynamically significant coronary artery disease patients. We, also, correlate the coronary anatomy to predict the false positive stress test response in patients with or without atherosclerotic risk factors.
MATERIALS AND METHODS
This is a prospective, single center, observational study. We analysed a total 200 patients (N=200), who were scheduled for coronary angiography after positive response for reversible provable ischaemia on TMT. Patients with known coronary artery disease, chronic renal failure, chronic liver disease, chronic heart failure, valvular heart disease and patients with known contraindications to stress test were excluded from study.

Treadmill Testing
The TMT was performed according to the standard Bruce protocol. Before testing, detailed history and physical examination was done as standard protocol in all participants. Participants with, acute myocardial infarction, within 2 days, high risk unstable angina, uncontrolled cardiac arrhythmias symptomatic severe aortic stenosis, decompensated heart failure, known case of CAD, complete heart block and hypertrophic cardiomyopathy with severe resting gradients were excluded from study. A resting 12-lead electrocardiogram (ECG) was taken before starting the test and then ECG was continuously monitored. An ECG print-out was obtained whenever any abnormality was detected, and at the completion of each stage, immediately after the exercise and at each minute in the recovery phase. In addition, an ECG was printed when patient complained of chest pain. Blood pressure was monitored during last minute of each stage or at least every 3 minutes. Recovery time of >6 minutes was usually allowed if no ST-segment changes were present or exercise evoked ST changes disappeared during this time. In other cases, the recovery phase was terminated when ST-segment normalization was achieved, and/or the heart rate slowed to <100 beats/minute.

Horizontal or down sloping ST-segment depression >1 mm 60 to 80 m sec after the J point (60 millisecond post-J point criteria is used at HR higher than >130 beat/minutes) in three consecutive beats on two or more contiguous leads corresponding to any myocardial wall was considered as positive TMT. Considering all leads, ST-segment depression of >1 mm were summed.

Blood pressure (BP) was measured by the Korotkoff method using a mercury sphygmomanometer. The BP measurements were taken at rest and during the last minute of each exercise stage, including recovery.

The TMT was terminated either because of the patient’s request to stop, because of moderate to severe angina limiting exercise continuation, complex ventricular arrhythmia (ventricular bigeminy, ventricular runs or ventricular tachycardia), new bundle branch block, Central nervous system symptoms, sign of poor perfusion (cyanosis or pallor), drop in systolic blood pressure of >10 mm Hg accompany by other evidence of ischaemia, physical exhaustion or any other disabling symptom (intermittent claudicating dizziness or dyspnoea). The TMT was also discontinued if no abnormal signs and symptoms were present but he patient’s heart rate (HR) exceeded 86% of the age adjusted limit. Duke treadmill score was calculated by following formula; Duke Treadmill score (DTS) = Exercise time - (5 x ST change) – (4 x angina index)

During TMT following Parameters were Compared-
1. Time to angina pain
2. Total METS achieved
3. Maximum of THR achieved
4. Total exercise time
5. Maximum ST segment depression
6. Maximum systolic and diastolic blood pressures
7. Average duke treadmill score (DTS)
8. Average METS at which ST-T abnormality started
9. Rate pressure product achieved
10.ST-HR indeed
11.Reasons to stop exercise.

Coronary Angiography
Coronary angiography was performed by a radial or femoral route using the Seldinger technique. Coronary arteries in posterior anterior, left and right oblique planes with necessary cranial or caudal angulations were analysed. Coronary arteries were considered to be normal on the basis of visual assessment of the absence of any luminal irregularities.

Coronary angiograms were analysed, by multiple observers who was blinded to the echocardiographic and clinical data, for the type of the LAD, the presence and severity of coronary artery disease (CAD), and dominance of the coronary circulation. The visual grading system was used to determine the length of the LAD. CAD was defined as the presence of any atherosclerosis on the angiogram, and obstructive disease as the presence of more than 50% stenosis in any major epicardial artery more than 1.5 mm in diameter.

LAD Length was Graded into Four Types as Following-
Type 1- LAD falls short of left ventricular (LV) apex
Type 2- LAD reaches up to the LV apex,
Type 3- LAD supplies the entire apex,
Type 4- LAD supplies the apex and >25% of the inferior wall (warp around).

RESULTS
Out of total 200 patients, 70 patients were having normal coronary arteries on CAG and rest 130 patients were suffering from hemodynamically significant CAD. The baseline characteristics of these two study groups were enlisted in the table 1. Compared to CAD population, most of the cardiac syndromes X patients were of female sex, obese and lesser CAD risk factors.
Parameters | Syndrome X (n=70) | CAD (n=130)
--- | --- | ---
Baseline Parameters
Age (Mean ± 2SD) | 52 ± 6 | 58 ± 8
Male (%) | 20 (28.57%) | 90 (69.23%)
Female (%) | 50 (71.42%) | 40 (30.76%)

Risk Factors
1. Smokers (%) | 16 (22.82%) | 58 (44.60%)
2. Diabetes Mellitus (%) | 9 (12.85%) | 32 (24.61%)
3. Hypertension (%) | 21 (30.60%) | 60 (46.15%)
4. Peripheral Vascular Disease | 0 (0%) | 12 (9.23%)
5. Body Mass index >25 Kg/m2 (%) | 16 (22.85%) | 18 (13.84%)
6. Dyslipidaemia (total cholesterol >200 mg% (%)) | 12 (17.14%) | 36 (27.69%)
7. Family history of premature CAD in 1st degree relative (%) | 0 (0%) | 8 (6.15%)
8. Alcohol % | 8 (11.42%) | 32 (24.65%)
9. Lack of exercise | 16 (22.85%) | 28 (21.53%)

Table 1. Baseline Characteristics of the Study Participants

Angiographic characteristics of the study participants were enlisted in the table 2. Compared to CAD population, most of the cardiac syndromes X patients were having type 2 LAD creating LV apex as a relatively ischaemic zone.

Parameters | Syndrome X (n=70) | CAD (n=130)
--- | --- | ---
Type of CAD
1. Normal Coronary Arteries (%) | 70 (100) | 0
2. Single Vessel Disease (%) | 0 | 68 (52.30%)
3. Double Vessel disease (%) | 0 | 32 (24.61%)
4. Triple Vessel disease (%) | 0 | 30 (23.07%)
Type of Left Anterior Descending (LAD) Artery
5. LAD type II (%) | 20 (28.57%) | 21 (16.15%)
6. LAD type III (%) | 50 (71.42%) | 109 (83.84%)

Table 2. Angiographic Characteristics of the Study Participants

Exercise test parameters of the study participants were enlisted in the table 3. Compared to CAD population, most of the cardiac syndromes X patients were having favourable prognostic factors.

Parameters | Syndrome X (n=70) | CAD (n=130)
--- | --- | ---
Exercise TMT Parameters
1. Total METS achieved (mean) | 7.12 | 7.19
2. Maximum SBP (mean) | 168 | 164
3. Maximum DBP (mean) | 84 | 89
4. Average Duke Treadmill Score (DTS) | -2 | -11
5. Average METS at which ST-T abnormality started | 6.3 | 3.2
6. Mean HR at which ST-T abnormality started | 142 | 132
7. Maximum of THR achieved (mean) | 96 | 106
8. Rate-pressure product achieved (mean) | 23963 | 23454
9. ST-HR index (mean) | 6.6 | 21.2

Table 3. Exercise Test Parameters of the Study Participants

Atypical symptoms like fatigue, shortness of breath and leg cramps were the limiting factors to stop the exercise in cardiac Syndrome X population whereas more malignant feature like angina pain associated with ST-T wave changes was the limiting factor in CAD population (table 4).
Diabetes mellitus can affect the heart, increasing the risk of developing coronary artery disease and heart failure. Patients with diabetes often have dyslipidemia, high blood pressure, and hyperglycemia, which can result in atherosclerosis and coronary artery disease. The severity of coronary artery disease is more extensive than in non-diabetic patients. In addition, the myocardium of diabetic patients is more susceptible to ischemia because of endothelial dysfunction and reduced vasodilation. Thus, the diagnosis of coronary artery disease in diabetic patients may be more challenging and require a higher diagnostic yield of hemodynamically significant CAD. The diagnostic yield of stress testing in diabetic patients is lower compared to non-diabetic patients, resulting in a greater number of patients requiring additional imaging modalities to confirm watershed zones as the culprit arteries.

### DISCUSSION

Mechanism of Cardiac Syndrome X has not been defined but several clinical studies have proposed impaired coronary flow reserve and impaired pain perception due to autonomic dysfunction as the pathogenesis of this syndrome, several studies have demonstrated perfusion abnormalities with radionuclide techniques in these patients.

Up to 30% of the patients who underwent coronary angiography to evaluate the cause of chest pain have angiographically normal coronary arteries. The term, cardiac Syndrome X, first used by Kemp et al. in 1973 to describe a group of patients with typical angina and normal coronary angiograms, is now widely used to specify patients with angina like chest pain, ischaemia like ECG, normal coronary angiograms, and no evidence of coronary spasm. Chest pain in patients with cardiac Syndrome X is usually exertional and have similar properties to that in patients with coronary artery disease. Although the underlying pathophysiology has not been clearly defined, cardiac Syndrome X is characterized by two major abnormalities, coronary microvascular dysfunction, and abnormal cardiac pain perception or sensitivity. The coronary microvascular dysfunction may be associated with either the reduced coronary microvascular dilatory response to variable physiological and pharmacological stimuli (exercise, adenosine, dipyridamole, and atrial pacing) or the increased coronary resistance at rest, or both, which may explain the abnormal behavior of the coronary microvasculature in cardiac Syndrome X. On the other hand, increased pain perception is common in patients with cardiac Syndrome X. Potassium and nandosinone release, as well as abnormalities is the central modulation of pain perception, have been suggested to play a role.

We also hypothesized that ischaemia at zone of two coronary vessels may be one of the precipitation factors contributing to myocardial ischaemia. This is further supported by the fact that most of our patient with normal coronary arteries were having type 2 LAD, creating LV apex as a relatively ischemic zone. Similarly, watershed areas at other coronary arteries meeting point may be responsible for positive response to exercise stress test. Favourable TMT parameters like greater METS achieved, lesser DTS and ST-HR index and appearance of ST-T wave abnormalities at greater METS or HR giving clues that in these patient groups myocardium has greater threshold for coronary ischaemia at watershed zone. Moreover, coronary ischaemia is manifesting as objective signs of repolarization abnormality (ST-T wave changes) rather that subjective sensation of chest pain. This hypothesis needs further validation by other imaging modalities to confirm watershed zones as the culprit zones for positive exercise test.

### CONCLUSION

Favourable TMT parameter like greater METS achieved, lesser DTS and ST-HR Index, appearance of ST-T wave abnormalities at greater METS or HR decreases the diagnostic yield for hemodynamically significant CAD, whereas angina pain with ST-T changes increased the diagnostic yield of hemodynamically significant CAD.

### REFERENCES


