**Original article**

# Risk profile in asymptomatic first degree relatives of Coronary Artery Disease (CAD) patients.

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**Abstract**

***Aim:*** Cardiovascular disease is on the rise and is expected to be a leading cause of death and disability worldwide. Identification of risk in asymptomatic individual in higher risk group could help to plan individual patient's management. Positive family history is one of the risk factors and screening at this level may help in determining individual therapy. Studies have shown relation of positive family history but are lacking in this part of world, so we considered it worthwhile to assess FRS in asymptomatic sibling of CAD Patients ***Materials and methods:*** 75 volunteers were enrolled in the study and they underwent Bruce treadmill exercise protocol after their initial evaluation, these volunteers than also underwent biochemical test – Fasting blood sugar and lipid profile. These volunteers were divided into two groups based upon their Treadmill test results. ***Results:*** 31 out of 75 volunteers were TMT positive and they were kept in one group. These volunteers differed significantly ($p<0.05$) in higher age, fasting blood sugar and Low density lipoprotein level (LDL). This group also had a significantly lower metabolic equivalents and higher Framingham Risk Score. ***Conclusion:*** Our study showed that positive family history is associated with a higher Framingham risk score in asymptomatic volunteers.

**Keywords:** Coronary artery disease, Treadmill test, Framingham risk score, fasting blood sugar, lipid profile

## Introduction

The burden of cardiovascular diseases (CVD) is increasing worldwide, with a sharp rise in the incidence and prevalence in the developing countries. India is now in the middle of a coronary artery disease (CAD) epidemic and CAD is expected to be the leading cause of death and disability adjusted life years (DALYS) lost by the year 2020[1,2]. The reason postulated for higher prevalence of CAD in Indians is increased genetic propensity and increasing prevalence of cardiovascular risk factors[3,4]. Traditional risk factors that comprise the Framingham Risk Score (FRS) are the foundation for estimating risk in asymptomatic individuals[5].

Improved identification of asymptomatic individuals in higher risk group is an important health issue, both for the planning of strategies of individual patient management and, to decrease the community cost associated with unrecognized coronary heart disease. Selection of a higher risk group for screening provides a higher prevalence of disease in those screened and thus increases the predictive value of a positive test result[6].

Exercise testing may provide valuable prognostic information in asymptomatic individuals who have risk factors[7] recommend screening in asymptomatic higher risk group only and suggests that exercise tolerance testing will probably perform better when applied to higher risk groups such as persons with one or more risk factors for CAD.

The National Cholesterol Education Program and Framingham Data have considered positive family history in defining risk status[8,9]. Thus, it has been

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suggested that asymptomatic adults with a positive family history may benefit from subclinical disease screening to determine the need for primary preventive therapies[10]. Some studies conducted across the globe have found Exercise induced ECG suggestive of ischemic changes present in apparently healthy siblings of CAD patients[11,12]. There are insufficient studies conducted in India on healthy siblings of CAD patients, hence we designed this pilot study to provide the preliminary data of risk factors in asymptomatic first degree relatives of CAD patients.

## Materials and Methods

### Subjects:

This prospective study was conducted in the Departments of Physiology and Cardiology, Christian Medical College and Hospital, Ludhiana on asymptomatic first degree relatives (defined as the individual who is one meiosis away from the subject i.e. the parents, the offspring's or the siblings) of Coronary Artery Disease patients. The definition of CAD included myocardial infarction, stable angina, and coronary insufficiency.

Only those first degree relatives above the age of 20 years were included in the study who had never suffered with symptoms suggestive of CAD. A subject with known heart disease or one with any contraindication to exercise testing (e.g. physical impairment, acute or chronic severe pulmonary disease, acute ongoing febrile disease etc.) were excluded from the from the study.

The study was approved by the Institutional Ethics Committee (IEC) of Christian Medical College and Hospital and conducted in accordance with ICH-GCP guidelines. All subjects were enrolled in the study only after obtaining written informed consent.

### Method

Baseline data was collected for each participant in the study including age, sex, Body Mass Index (BMI), relationship with CAD patients, and history of smoking, diabetes, hypertension and various biochemical tests – fasting blood sample for estimation of fasting blood sugar (FBS) and Lipid profile.

All the participants in the study underwent standard Bruce treadmill protocol exercise tests[13]. The test was terminated when a predetermined target heart rate of ? 85% of maximum predicted heart rate for age and physical activity was attained or because of appearance and excessive progression of symptoms, exhaustion or development of marked ST segment deviation or significant ventricular arrhythmia.

Main end points for exercise recorded according to Bruce Protocol were total exercise time expressed in seconds, peak exercise capacity expressed in Metabolic Equivalents (METs) and ischemic Electrocardiographic (ECG) changes. The result of the test was recorded as negative, inconclusive or positive. Positive tests were defined as showing ? 1 mm of flat or down-sloping ST depression in any of the standard ECG leads. Inconclusive tests were defined as not meeting the positive test criteria but showing concerning change (e.g. symptoms of chest pain without ECG change of ischemia or inadequate exercise time or inability to achieve target heart rate).

Sex-specific Framingham equations for 10-year absolute risk of hard CAD events (myocardial infarction or CAD death) based on AHA Scientific Statement were used to calculate FRS values[14].

Serum lipid levels were determined from the fasting samples from visit Smoking was defined as smoking tobacco at visit Hypertension was defined as baseline systolic blood pressure ? 140 mm Hg, diastolic pressure ? 90 mm Hg or treatment for hypertension.

### Statistical analysis:

Data are presented as mean ± standard deviation for continuous variables and as frequency for categorical variables. Comparisons of continuous variables were performed using the Student's or paired t-test. Analyses of discrete variables were performed using the?$^2$ test or Fisher's exact test where appropriate. The assumed covariance structure was compound symmetry which made the best fit for the data. The Bonferroni correction was performed for post-hoc comparisons. Statistical analyses were performed using SPSS, version 11.0. All tests were two-sided and a P-value of $< 0.05$ was considered statistically significant. As this was not a randomized study to compare the outcome of two different strategies, sample size calculation to establish a powered analysis was not performed.

## Results

A total of 75 volunteers who were first degree relatives of coronary artery disease patients admitted in Coronary Care Unit or attending the Cardiology

O.P.D were included in the study. These volunteers underwent standard Bruce treadmill protocol exercise tests. Main end points for exercise recorded according to Bruce Protocol were total exercise time expressed in seconds, peak exercise capacity expressed in METs and ischemic ECG changes.

Ischemic-type ST-segment abnormalities were observed during and/or after exercise in 31(41.3%) of the 75 volunteers (Table I).

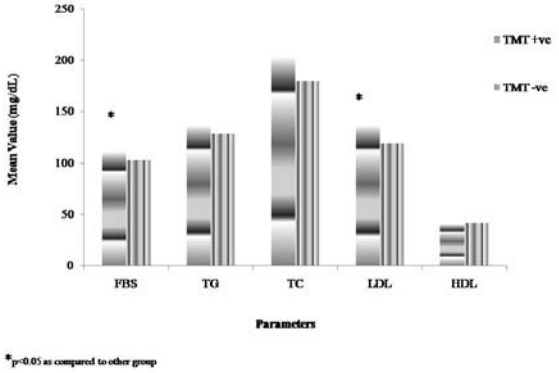
Table I. Treadmill exercise test parameters in both the groups.

| TMT parameter | TMT positive (Mean ± SD) | TMT negative (Mean ± SD) |
|---|---|---|
| Exercise Time (s) | 309 ± 136 | 454 ±134 |
| Metabolic Equivalents | 6.38 ± 2.06 | 8.72 ± 2.32 |
| Percentage of Target Heart rate Achieved | 91 ± 15 | 96 ± 11 |
| Maximum ST Segment Depression (mm) | 141 ± 86 | 83 ± 70 |

One male sibling had exercise-induced hypertension. No individual experienced typical anginal chest pain during the test. 96% of siblings achieved >85% of the maximal predicted age-adjusted heart rate. The healthy volunteers were divided into two groups based on the TMT results and were compared. Although all the demographic characteristics were higher in TMT positive group (Table 2) but, both the groups were comparable in all the parameter except for age, which was significantly higher in volunteers with TMT positive results (44.48 ± 12.17 vs. 50.1 ± 11.28). The other factor like Smoking behavior was comparable in both the groups. The number of males and females were comparable in both the groups (Table II).

Profile. Total Cholesterol (TC), Triglycerides levels (TG), Low Density Lipoproteins levels (LDL), High Density Lipoprotein levels (HDL) were estimated in Lipid profile. The TG levels, and TC levels, were higher in TMT positive group whereas the HDL levels were lower in TMT positive group, but were comparable in both the groups. Although the LDL level was significantly more in the volunteers who were TMT positive (136.4 mg/dL vs. 118.8 mg/dL), similarly the FBS level was significantly more in volunteers who were TMT Positive (110.9 mg/dL vs. 102.5 mg/dL) (Figure I).

Figure I. Comparison of Mean biochemical parameters in both the groups




**Framingham Risk Score:**

FRS which depends on age, gender, diabetes, total cholesterol, HDL, smoking and systolic blood pressure was estimated in both the groups. Framingham risk score was significantly higher in volunteers who were TMT positive (6.97 in TMT positive group vs. 3.02 in TMT negative group) and metabolic equivalent was significantly lower in TMT positive group (6.38 in TMT positive group vs. 8.72 in TMT negative group) (Figure 2). The mean MET was significantly lower in TMT positive group as compared to TMT negative group (6.38 in TMT positive Group vs. 8.72 in TMT negative group) (Figure 2).

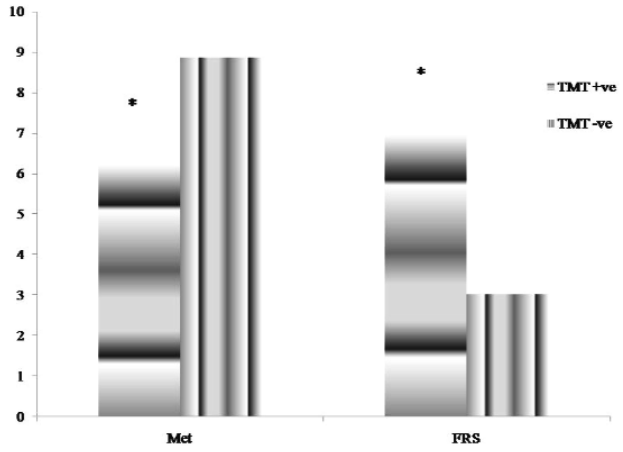
Table II. Demographic characteristic of Healthy Volunteers.

| Parameter | TMT negative (n=44) | TMT Positive (n=31) |
|---|---|---|
| Age (years) (Mean ± SD) | 44.48 ± 12.17 | 50.1 ± 11.28* |
| Sex (M:F) | 33:11 | 16:15 |
| Smokers | 10 | 10 |
| Weight (Kg) (Mean ± SD) | 71.77 ± 11.06 | 73.54 ± 13.67 |
| Height (meters) (Mean ± SD) | 1.63 ± 0.06 | 1.61 ± 0.08 |
| Body Mass Index (kg/m$^2$) (Mean ± SD) | 27.43 ± 4.16 | 28.61 ± 5.142 |
| Systolic Blood Pressure (mm of Hg) (Mean ± SD) | 127.75 ± 11.0 | 132.26 ± 10.23 |
| Diastolic Blood Pressure (mm of Hg) (Mean ± SD) | 81.05 ± 9.14 | 83.81 ± 8.94 |
| *p<0.05 as compared to other group | | |

**Biochemical tests:**

Fasting Blood Samples were taken for biochemical tests like Fasting Blood Sugar (FBS) and Lipid

Figure 2. Comparison of FRS and MET in both the groups




## Discussion

To slow the momentum of CAD in countries such as India, particularly among the working-age population, major initiatives are needed to combat CAD, whether promotion of diet and physical activity, generation of awareness or development of guidelines for risk factors and therapeutic and surgical strategies.

A family history of premature CAD is a strong risk factor and some studies have pointed out that this screening is rarely performed in daily clinical practice[15,16]. We believe that people who have a dear one suffering from the disease are more receptive for making positive changes to stay away from disease. Our study supports that positive family history of CAD is associated with increased risk of coronary artery disease as various parameters suggestive of higher future risk for developing coronary artery disease were present in our study group which were asymptomatic at the time of study and thus are discussed below.

Exercise induced ECG changes suggestive of ischemic changes were present in 41% of the study participants which is more than what has been reported in two studies. One study reported that 21% of apparently healthy sibling of CAD patients showed TMT positive results[12], whereas the other study demonstrated ischemic changes in 19% of subjects[11].

It has been widely documented that the risk of developing coronary heart disease and premature atherosclerosis increases, as the level of serum cholesterol rises[17-19] and in our study these mean values were higher in the TMT positive group and the LDL cholesterol levels was significantly higher.

If Framingham risk scores alone are used to identify persons for aggressive therapy, most siblings with occult CAD would fail to be targeted and would not be treated with lower goal levels, which are recommended for those with CAD [12].

This study's strength is that it differs from indiscriminate testing of asymptomatic subjects in that those tested had, at least one first degree relative suffering from established CAD and suggests that when such a susceptible population is screened, the pretest likelihood is increased in terms of identification of unrecognised CAD. And at the same time the approach, has the potential to provide a cost-effective way of screening for coronary heart disease in the community. Although the risk of siblings developing CAD is much higher than that of the general population, current guidelines do not target such families for aggressive preventive efforts. Targeted testing in high-risk families clearly identifies individuals with occult CAD Consistent with previous studies, our results demonstrated that the first degree relatives of patients with premature CAD had an increased prevalence of individual risk factors and a higher overall risk of future coronary events. Thus we suggest family history evaluation with subsequent feedback to participating family members has great potential for educating and motivating entire populations about their familial health risks and increasing awareness about the importance of preventive health practices[7].

## Conclusion

The findings in our study may have important public health implications as there is a feasibility of using patients with premature CAD as a means by which to identify and contact people with high risk who are not currently screened. This strategy should be evaluated in large multicentre study.

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