

Original Research Article

Assessment of endothelial dysfunction in young healthy first-degree relatives with family history of premature coronary artery disease using vascular doppler ultrasonography

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ABSTRACT

Background: Endothelial dysfunction in young healthy first-degree relatives with family history of premature coronary artery disease was assessed in the present study using vascular doppler ultrasonography.

Methods: Thirty young (10-40 years) first degree relatives of 17 patients with premature CAD without risk factors were selected for the study. Age and gender matched healthy subjects were enrolled as controls. Non-invasive assessment of endothelial dysfunction was done by vascular doppler study of brachial artery. Brachial artery diameter, velocity and blood flow were estimated in every study subject and control at rest, after stress and again at rest and after glyceryl-trinitrate (GTN) by vascular Doppler ultrasonography.

Results: The percent rise in lumen diameter of brachial artery after stress i.e. reactive hyperaemia, labelled as percent rise in flow mediated dilatation (FMD), was significantly lower in family history group than in controls ($8.42 \pm 3.47\%$ vs $12.22 \pm 4.31\%$, $p < 0.05$). The statistically significant difference in percent rise in FMD was observed to be consistent across different ages/genders ($p < 0.05$). The mean percent rise in FMD among family history group with positive maternal history (8.06 ± 3.65) was lower as compared to those with positive paternal history (8.57 ± 3.12), but the difference was not statistically significant ($p > 0.05$).

Conclusions: Apparently healthy young subjects with family history of premature CAD have impaired endothelium dependent FMD in systemic circulation. Simple, non-invasive, cost-effective vascular doppler ultrasonography is recommended as a potential screening tool to detect subclinical atherosclerosis.

Keywords: Endothelial dysfunction, Family history of premature CAD, Young healthy first degree relative, Vascular doppler ultrasonography

INTRODUCTION

In India, non-communicable diseases (NCDs) have taken over the infectious diseases, diseases of undernutrition, and maternal and childhood diseases in a relatively short timeframe.¹ Cardiovascular diseases (CVDs) have been contributing to the all-cause mortality in India in major

way for a while now.² CVD occurs and behaves in more disturbing manner by affecting Indians at least a decade earlier and in their most productive years.^{3,4} Ischemic heart disease (IHD) constitutes the majority of CVD mortality in India (83%).⁵ The prevalence of IHD in urban India increased 7-fold to $\approx 14\%$ and quadrupled in

rural areas to 7.4% during similar period of last four decades, indicating public health failure at large.⁶⁻⁸

As per the Framingham heart study, the presence of cardiovascular risk factors like hypertension, hypercholesterolemia, diabetes mellitus, smoking and obesity play an important role in subsequent development of atherosclerosis and coronary syndromes. Endothelial dysfunction (ED) has been the common pathogenic mechanism implicated. It is an initiating event for atherosclerosis.⁹ In about 30-50% of cases, the traditional risk factors have been reported to be absent; which argues for actively looking for newer predictive factors.¹⁰ Because the endothelium may be a target that integrates the damaging effects of the traditional and unknown risk factors, it has been proposed as a potential barometer of atherosclerotic risk, and as such, studying endothelial function may guide risk assessment and therapy for individuals. Indeed, studies are being done to identify ED at an early stage.

Parenteral history is an important surrogate measure for cardiovascular risk in the offspring.¹¹ It has been demonstrated that young healthy first degree relatives with a family history of premature coronary disease may have impaired endothelium dependent dilatation, even in absence of other cardiovascular risk factors.¹² One can attempt to detect this either by coronary angiography, but that is not a feasible screening tool plus, more importantly, ED is known to exist even in angiographically normal vessels. ED has been postulated to be demonstrated by simple non-invasive methods to unearth subclinical atherosclerosis. With the present study, endothelial dysfunction in young healthy first-degree relatives with family history of premature coronary artery disease was assessed using vascular doppler ultrasonography.

METHODS

A hospital based prospective observational study was done in the department of Medicine, tertiary care government institute. Study period was more than one and half years from June 2003 to February 2005. A total of 60 participants were studied (30 cases and 30 controls).

Premature coronary artery disease (CAD) was defined as occurrence of CAD in men <45 years and women <55 years of age.¹³ A total of 40 patients with premature CAD following above criteria were admitted during the study period. Detailed history, clinical examination and biochemical investigations revealed 17 of them without risk factors of hypertension, diabetes mellitus, dyslipidemia, smoking and obesity. In the next step, 30 young (10-40 years) first degree relatives of only these 17 patients were selected for the study. Age and gender matched healthy subjects (without risk factors and in whom the family history of IHD at any stage in first degree relatives was absent) were enrolled as controls.

Information was collected through pre-set proforma from each participant. Detailed history and careful physical examination were done with special reference to hemodynamic parameters like jugular venous pulse (JVP) and blood pressure etc. They were also evaluated for coronary risk factors like diabetes mellitus, hypertension, smoking, obesity, alcohol and dyslipidemia. In all of them 12-lead ECG, fasting and post-meal blood sugar levels, 12-hours fasting serum lipid profile were done. Non-invasive assessment of endothelial dysfunction was done by vascular Doppler study of brachial artery. Brachial artery diameter, velocity and blood flow were estimated in every study subject and control at rest, after stress and again at rest and after glycertrinitrate (GTN) by vascular Doppler ultrasonography.

The study was commenced after approval from institutional ethics committee. Informed written consent was elicited from each participant.

RESULTS

The present study was conducted on 30 young healthy first-degree relatives of patients with premature CAD and 30 age and gender matched controls over one and half year's study period and incorporated studying endothelial dysfunction using vascular doppler ultrasonography. Seventeen patients with premature CAD but without risk factors of hypertension, diabetes mellitus, dyslipidemia, smoking and obesity were identified during study period. In the next step, 30 young (10-40 years) first degree relatives of only these 17 patients (Family history group-group A) and their age and gender matched controls (control group-group B) were studied further.

The mean age of participants was 22.13±4.98 years and 21 participants (70%) in each group were males. Fifteen participants in group A (50%) and 16 participants in group B (46.67%) were overweight with BMI >25kg/m², the difference between their means being insignificant (23.98±3.77 kg/m² vs. 25.24±2.83kg/m², p>0.05).

The systolic (117.8±10.3 mmHg vs. 117.27±9.43mmHg) and the diastolic blood pressure values (74±4.98 mmHg vs. 75±5.08mmHg) were comparable between groups. Similarly, fasting and post-meal blood sugar values (85.1±5.65mg/dl vs 84.36±6.71mg/dl and 134±16.8mg/dl vs 134.63±15.28mg/dl) and none of the parameters of the Lipid profile were either abnormal or varied statistically significantly between the two groups (p>0.05), as detailed in (Table 1).

Various parameters of endothelial functions on vascular doppler ultrasonography were compared between groups. No significant difference was observed for characteristics of brachial artery like diameter at rest, velocity at rest, blood flow at rest, diameter after GTN, percent rise in lumen diameter of brachial artery after GTN, diameter during reactive hyperemia, velocity during reactive

hyperemia, blood flow during reactive hyperemia and percent rise in blood flow during hyperemia ($p>0.05$).

Table 1: Baseline physical and biochemical characteristics of study participants.

Characteristics	Family history group (group A) (Mean \pm SD)	Control group (group B) (Mean \pm SD)	P value
Systolic BP (mmHg)	117.8 \pm 10.3	117.27 \pm 9.43	>0.05
Diastolic BP (mmHg)	74 \pm 4.98	75 \pm 5.08	>0.05
Fasting blood sugar (mg/dl)	85.1 \pm 5.65	84.36 \pm 6.71	>0.05
Post-meal blood sugar (mg/dl)	134 \pm 16.8	134.63 \pm 15.28	>0.05
Lipid profile (mg/dl)			
HDL	38.66 \pm 6.27	38.86 \pm 5.39	>0.05
LDL	98.93 \pm 14.13	93.33 \pm 7.72	>0.05
VLDL	28.40 \pm 4.94	30.60 \pm 5.84	>0.05
TG	103.27 \pm 15.56	101.07 \pm 13.04	>0.05

Table 2: Endothelial function characteristics on vascular doppler ultrasonography.

Characteristics	Family history group (group A) (Mean \pm SD)	Control group (group B) (Mean \pm SD)	P value
Brachial artery diameter at rest (mm)	3.77 \pm 0.35	3.75 \pm 0.33	>0.05
Brachial artery velocity at rest (cm/sec)	35.73 \pm 7.58	38.16 \pm 6.74	>0.05
Brachial artery blood flow at rest (ml/min)	236.36 \pm 46.15	249.6 \pm 38.83	>0.05
Brachial artery diameter during reactive hyperaemia (mm)	4.08 \pm 0.42	4.21 \pm 0.43	>0.05
Brachial artery diameter after GTN (mm)	4.41 \pm 0.53	4.34 \pm 0.45	>0.05
Brachial artery velocity during reactive hyperaemia (cm/sec)	75.63 \pm 6.07	75.46 \pm 4.5	>0.05
Brachial artery blood flow during reactive hyperaemia(ml/min)	559.75 \pm 89.37	600.99 \pm 105.91	>0.05
Percent rise in FMD	8.42 \pm 3.47	12.22 \pm 4.31	<0.05*
Percent rise after GTN mediated dilatation	16.87 \pm 6.38	15.97 \pm 5.49	>0.05
Percent rise in blood flow during hyperaemia	244.58 \pm 57.09	240.99 \pm 51.08	>0.05

*- Statistically significant

However, the percent rise in lumen diameter of brachial artery after stress i.e. reactive hyperemia, labelled as percent rise in flow mediated dilatation (FMD), was significantly lower in family history group than in controls (8.42 \pm 3.47% vs 12.22 \pm 4.31%, $p<0.05$) (Table 2).

When endothelial function was further compared across different age groups, the mean percent rise in FMD of family history group (group A) was 8.38 \pm 4.24 in age group 10-19 years, was 8.24 \pm 2.98 in 20-29 years and was 8.83 \pm 5.71 in 30-40 years. In control group (group B), the mean percent rise in FMD was 13.02 \pm 5.92 in age group 10-19 years, 11.38 \pm 3.38 in 20-29 years and was 14.85 \pm 3.52 in 30-40 years. Thus, the statistically significant difference in the percent rise in FMD was observed to be consistent across different age groups ($p<0.05$). However, the intragroup difference between the three age classes amongst the family history group didn't indicate any trend and was statistically insignificant ($p>0.05$).

Gender-wise analysis revealed the mean percent rise in FMD in males in family history group to be significantly lower as compared to control males. (8.12 \pm 3.72 vs 11.7 \pm 3.57, $p<0.05$). Similar findings of significantly lower mean percent rise in FMD were observed in

females as well (9.13 \pm 2.9 vs 13.45 \pm 5.28, $p<0.05$). However, the intragroup gender-wise analysis revealed insignificant difference between males and females in the family history group (8.12 \pm 3.72 in males vs 9.13 \pm 2.9 in females, $p>0.05$).

The family history group was further analyzed with regards to the maternal and paternal family history and BMI. The mean percent rise in FMD among family history group with positive maternal history (8.06 \pm 3.65) was lower as compared to those with positive paternal history (8.57 \pm 3.12), but the difference was not statistically significant ($p>0.05$).

DISCUSSION

Ischemic heart disease (IHD) is an epidemic of increasing proportions and atherosclerosis remains the major pathology in IHD. History of premature coronary artery disease (CAD) in a first degree relative is an established independent risk factor for CAD.^{14,15} More and more efforts are being put into demonstrating the presence of subclinical atherosclerosis in such high risk individuals as evidenced by endothelial dysfunction (ED) in systemic arteries occurring in preclinical phase of vascular disease and a family history of premature CAD is included in clinical guidelines for the prevention of coronary heart

disease.¹⁶ With this thought in mind, the present study was aimed at picking up endothelial dysfunction in young healthy first degree relatives with family history of premature coronary artery disease using vascular doppler ultrasonography. Thirty young healthy first-degree relatives of patients with premature CAD and 30 age and gender matched controls (without family history of CAD) were studied over one and half year's study period.

The mean age of participants in present study (22.13±4.98 years) is comparable to previous similar studies.^{11,12,17} Since protective effect of estrogen diminishes in postmenopausal period, only premenopausal women (age<40 years) were recruited.¹⁸ There was insignificant difference between the mean BMI in the two groups, a finding also observed by Gaeta G et al, and Hashimoto M et al.^{17,19} Both the family history group and the control group participants had normal mean blood pressure and blood sugar levels as well normal mean lipid profile values. The values didn't vary significantly between the two groups as well. The normalcy of values is only logical given the age group studied and the statistical indifference is also mostly in line with what has been observed by most of the researchers previously.^{11,12,17,19}

The two groups were identical when compared for baseline characteristics like diameter at rest, velocity at rest, blood flow at rest, diameter after GTN, percent rise in lumen diameter of brachial artery after GTN, diameter during reactive hyperemia, velocity during reactive hyperemia, blood flow during reactive hyperemia and percent rise in blood flow during hyperemia. The percent rise in lumen diameter of brachial artery after stress i.e. reactive hyperemia, labelled as percent rise in flow mediated dilatation (FMD) was the only endothelial function parameter significantly lower in family history group than in controls (8.42±3.47% vs 12.22±4.31%, p<0.05). This finding suggest that endothelium dependent vasodilatation is significantly lower in the family history group as compared to controls; but endothelium independent vasodilatation is not significantly different. Most of the previous similar studies have reported similar baseline characteristics on vascular doppler ultrasonography.^{11,12,17} Our significant finding is in concordance with the strikingly similar study by Gaeta G et al, who had studied endothelial function non-invasively in 40 healthy off springs of patients with premature CAD.¹⁷ They had also reported off springs of premature CAD patients as having less percent rise in FMD as compared to age and sex matched controls.¹⁷ This point towards endothelial dysfunction in the subjects with family history. However, the cut-off values of percent rise in FMD for the endothelial dysfunction could not be calculated in the present study due to relatively small number of study subjects; prompting us here to suggest further similar studies with larger numbers.

Studies have shown the endothelial dysfunction to deteriorate with aging.^{20,21} The age-wise break-up of

endothelial function did reveal deterioration of endothelial function with increasing age in the first two age groups, albeit insignificantly. This trend didn't hold in the third age group of 30-40 years, probably due to very small number (n=3) of participants in the particular category. The gender-wise analysis of family history group revealed insignificant difference between males and females in the family history group (8.12±3.72 in males vs 9.13±2.9 in females). Taddei S et al, reported endothelial function to deteriorate by 0.57% per year in healthy females before the age of 49 years, whereas it deteriorated by 1.8% per year in males.²¹ Joannides R et al, had also reported males having significantly lower percent rise in FMD as compared to females.²² The reason for insignificance of results could again be attributed to the relatively smaller numbers.

Out of 30 subjects in the family history group, 15 had maternal history of CAD, 12 had paternal history and 3 had CAD in sister sibling. The mean percent rise in FMD in subjects with maternal history was insignificantly lower as compared to those with paternal history. Kinra S et al, observed paternal history of CAD to be at least as important as maternal history.²³ Intergenerational transmission of CAD does not appear to have differential effect between mothers and fathers.

CONCLUSION

In conclusion, the present study shows that apparently healthy young subjects with family history of premature CAD have impaired endothelium dependent FMD in systemic circulation. This is even when the subjects had no conventional risk factors for CAD among themselves and their affected first-degree relatives.

This suggests a direct inherited influence on arterial function that begins in the very young age which may herald the future risk of developing vascular disease. If one follows such subjects over long term for investigating clinical outcome, impaired FMD may act as phenotypic marker for those with inherited tendency to develop CAD. If it turns out to be so, then every effort should be made to detect it at the earliest in individuals at risk even if they are apparently healthy. Simple, non-invasive, cost-effective vascular doppler ultrasonography is recommended as a potential screening tool to detect subclinical atherosclerosis.

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