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Original Article

Endothelial Function in Adolescents with a History of Premature Coronary Artery Disease in One Parent

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ABSTRACT

Background: In young adults, a family history of premature coronary artery disease (CAD), as well as genetic and environmental factors are independent risk factors for coronary artery disease.

Methods: Endothelial function was studied in 30 children (21 boys and 9 girls with mean age of 14.9 +/- 2.3 years old)of patients with documented CAD (men ≤ 45 and women ≤ 50 years old). Chidren did not have any history of diabetes mellitus, dyslipidemia, hypertension, and smoking (active/passive). Using vascular ultrasound, we measured resting Basal Brachial artery Diameter (BBD) and Endothelium-Dependent Dilatation (EDD) in response to increased flow and sublingual glyceryltrinitrate (GTN), an Endothelium-Independent Dilation (EID). These parameters were also measured in 30 control subjects with normal parents (18 boys and 12 girls with mean age of 14.2 +/- 2/5years old) and results were compared with each other.

Results: Adolescents in CAD group had abnormal Endothelial Dependent Dilatation or EDD/BBD (8.5 +/- 3.4% vs 11.8 +/- 4.5% in control subjects; P= 0.003).Endothelial Independent Dilatation (EID/BBD) in the positive fimily history group was significantly more than control subjects (18.5 +/- 6.7% vs 11.9 +/- 5.2%; P <0.001). EDD/EID or the index of endothelial function was significantly lower in the positive family history group (0.92 +/- 0.05 vs 1+/- 0.03; P<0.001). There was no difference in EDD/EID index between those with history of premature CAD in mother (7 cases) and those with history of premature CAD in father (23 cases) (0.92 +/- 0.04 vs 0.91+/- 0.05).

Conclusion: Normal adolescents without any cardiovascular risk factors but a history of premature coronary artery disease in one parent may have endothelial dysfunction, and there is no difference whether the CAD is in mother or father.

***Keywords**:* Endothelial dependent dilation, family history, CAD risk factors, premature coronary artery disease

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Atherosclerosis is a diffuse process of the arterial tree that starts in childhood and early adult life1 Its preclinical stage may last for decades, during which time atherosclerotic changes progress slowly, and eventually causing lumenal stenosis 2, 3. It has been well known for several decades that subjects with a family history of myocardial infarction are at a higher risk of developing coronary artery disease 4-7. Several studies have shown that risk of coronary death in the first-degree relatives of coronary patients increases 2.5- to 7-folds in comparison to those without this background 8.

The key early event in atherogenesis is endo-thelial dysfunction, 2, 3 and the early marker of endothelial dysfunction is the loss of Endothelium Dependent Dilatation, thought to be related to reduced activity of NO 9, 10. This substance can not only induce vasodilation, but also possess antitrophic properties 11, 12. One of noninvasive tests for studing endothelial function is based on flow-mediated

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ultrasonic changes in arterial diameter in relatively superficial arteries, such as the brachial arteries [13]. This method correlates significantly with invasive testing of coronary endothelial function [13, 14], as well as with the severity and extent of coronary atherosclerosis [15].

In this study, we have evaluated a cohort of adolescents with history of premature CAD in one parent, in whom the potentially confounding risk factors were excluded to examine only the influence of family history on endothelial function.

Subjects and Methods

36 patients (27 men ≤ 45 years old, 9 women ≤ 50 years old) with premature CAD (angiographically documented ≥75 % stenosis of at least one epicardial coronary artery, or admission in CCU because of ST elevation/Q waves MI on surface ECG plus adequate rising of cardiac enzymes) were selected from angiography and coronary care unit records of two Isfahan hospitals, over a 9-month period. By using a questionnaire containing smoking, hypertension, diabetes mellitus and dyslipidemia history and family history of premature CAD, we assessed these cardiovascular risk factors in CAD patients. To exclude CAD in their spouse, they were asked about history of chest pain. If they had never experienced chest pain they were assessed with resting ECG and if it was completely normal their 10-18 years old children entered the study.

In the control group, both parents were asked about cardiovascular risk factors with the same questionnaire. If both of them had never experienced chest pain and their resting ECG were free of any abnormalities their 10-18 years old children were studied as control group.

The young adults in both positive family history and control groups were asked about history of lifelong smoking or passive smoking (history of current smoking in one parent at home)and if the response was positive, the child was excluded from our study (N=0 subject). After at least 5 minutes resting we measured supine blood pressure (BP) in all adolescents and if resting BP was <130/85, rest of study was continued (2 subjects in the case group were excluded because of their BP>130/85). Biochemical tests from venous blood samples were evaluated in 64 subjects (CAD and control groups) after a 12-hour overnight fasting for plasma glucose (Pars Azmoun kit; 2003), total cholesterol (Pars Azmoun kit; 2003), LDL cholesterol (Randox kit), and triglyceride (Pars Azmoun kit; 2003). In this study, HDL cholesterol, lipoprotein (a), fibrinogen and homocysteine levels were not measured. Those young adults with, FBS >110 mg/dl, total cholesterol >240mg/dl, LDL cholesterol >160mg/dl, and triglyceride >250mg/dl were excluded from study (4 subjects in the positive family history group were excluded because of their abnormal lipid profile but none in control group).

Brachial artery evaluation

We studied endothelial function of brachial artery by using a 7.5-MHz linear array transducer B-mode ultrasound (Dornier Ultrasoud system 1992) in supervise of an expert sonographist who was unaware of study subjects (as in previous studies) [2]. After resting for at least 10 minutes, brachial artery was imaged in a longitudinal section of 5 to 7cm above the elbow. To measure the diameter of artery the best view of the anterior and posterior wall layers were needed. Finding the best position of transducer to show brachial artery, we marked best point on the skin and the arm did not move thenceforth throughout study and depth and gain settings of machine were the same during study. After measurement of basal brachial artery diameter (BBD), to study Endothelium Dependent Dilatation, flow to brachial artery was increased by aid of pneumatic tourniquet distal to brachial artery around forearm which inflated to 250-300 mm Hg for 4.5 minutes .Second scan of brachial artery was imaged 60 and 90 seconds after releasing cuff and brachial artery diameter was measured (EDD). Then we waited for 10 to 15 minutes for vessel to returne to its baseline status. Again, brachial artery diameter (EID) was recorded,but this time, 3 to 4 minutes after

administeration of one puff (400 microgram)of sublingual GTN spray (Pohl-Boskamp Gmbl & Co-Germany) .The amount of increased diameter of Brachial artery in two situations (EDD and EID) were compared with resting diameter (BBD) as percent measurements (100%). The relation between two situations (EDD and EID) were compared with each other (EDD/ EID).

Results

The spss software was used for data entry and analysis. We showed variables as mean ± SD. Two sample t- test was used to compare the data in CAD and control groups. In two positive family history subgroups, means those whose fathers had premature CAD and those whose mothers had disease, we used one-way ANOVA to compare EDD/BBD and EID/BBD responses and EDD/EID index. The relationship between age and Basal Brachial artery Diameter (BBD), EDD/BBD, EID/BBD and EDD/EID index were studied by univariate and multivariate regression analysis .We considered P-value< 0.05 as statistical significance.

23 men and 7 women (total 30 patients) were selected as CAD group;28 subjects with angiographically establishid CAD and only 2 from coronary care unit.All of 30 control parents were selected as described previously.The coronary risk factors (DM, HTN, dyslipidemia, smoking, and family history of premature CAD) in the parents are as followes: In the control group, 96.7% of mothers were free from all risk factors, but in the subgroup of mothers with premature CAD ,100% of mothers had more than one risk factor (P<0.001). In the control group 80% of fathers did not have any coronary risk factors but in the subgroup; fathers with premature CAD, 91.3% had at least one risk factor (P<0.001). The most prevalent risk factor in this subgroup was dyslipidemia (73.2%).

Demographic characteristics of positive family history and control young adults were as follow:

There was no significant difference in age of young adults between CAD and control groups (14.9 +/- 2.3 versus 14.2 +/- 2.5 years old; P=NS), age of their mothers (38.8 +/- 5 versus 40.4 +/- 5.7 years old; P=NS), and age of their fathers (44.5 +/- 5.8 versus 45.7 +/- 6 years old; P=NS) (Table 1). In comparison of the CAD group and its matched control group, the number of male subjects was much more than female ones in both groups (21 subjects or 70 % in CAD group and 18 ones or 60% in control group), but based on the Chi-Square test, distribution of gender variable, was equal in both above groups (P=0.417=NS).

Table 1. Age distribution in CAD and Control Groups.

	Premature CAD Group				Control Group				t-test	
	Mean	SD	Min	Max	Mean	SD	Min	Max	t	P
Child	14.9	2.3	10	18	14.2	2.5	10	18	1.1	0.137
Mother	38.8	5	30	48	40.4	5.7	28	50	1.2	0.120
Father	44.5	5.8	35	57	45.7	6	32	5 5	0.77	0.22

Cardiovascular Risk Factors

Biochemical tests characteristics in children with CAD history in parent and children of control subjects are shown in Table 2. FBS (91.4 +/- 7.9 versus 88.9 +/- 9.5 mg/dl; P=NS), total cholesterol (162 +/- 29 versus 159 +/- 25 mg/dl; P=NS), LDL cholsterol (66.3 +/- 26 versus 70 +/- 28 mg/dl; P=NS), and triglyceride(117 +/- 55 versus 122 +/- 49 mg/dl; P=NS); these amounts were not significantly different in the positive family history group and control group children.Four subjects in the case group were excluded because of hyperlipidemia. As shown in Table 2 the amount of SBP (112 +/- 10 versus 112 +/- 12.3; P=NS), and DBP (66 +/- 8.5 versus 66 +/- 7.6; P=NS)

Table 2. CAD risk factors in premature CAD and control groups.

	Premature CAD Group				Control Group				t-test	
	Mean	SD	Min	Max	Mean	SD	Min	Max	t	P
FBS	91.4	7.9	73	106	88.9	9.5	74	111	1.1	0.137
TC	162	29	121	250	159	25	113	217	0.39	0.348
LDL	66.3	26	30	132	70	28	28	123	0.62	0.268
TG	117	55	45	280	122	49	35	203	0.38	0.351
SBP	112	10	90	130	112	12	90	130	0.28	0.400
DBP	66	8.5	50	80	66	7.6	50	80	0.15	0.437

FBS=Fasting Blood Sugar; TC= total cholesterol; LDL=Low Density Lipoprotein;
TG=trigeliceride; SBP=Systolic Blood Pressure; DBP= Diastolic Blood Pressure

in the positive family history and control groups were the same. Two persons in the CAD group were submitted from the study since they had BP>130/85

Brachial artery avaluation

Basal Brachial artery Diameter (BBD) in CAD and control subjects offsprings was not different Table 3. Positive family history children, had markedly reduced Endothelium-Dependent Dilatation (EDD/BBD) (8.5 +/- 3.4% versus 11.8 +/- 4.5%, P=0.003); Endothelial Independent Dilatation (EID/BBD) in the CAD group was significantly more than control subjects (CAD subjects, 18.5 +/- 6.7%, and control subjects, 11.9 +/- 5.2%; P <0.001). EDD/EID or the index of endothelial function was significantly lower in the positive family history group 0.92 +/- 0.05 verssus 1+/- 0.03 in control subjects; P<0.001) (Table 3). EDD /EID index was compared in two subgroups of positive family history subjects; premature CAD in father and premature CAD in mother. Subjects with premature CAD in father had significantly impaired EDD/EID index in comparison to control group (0.91 +/- 0.05 versus 1+/- 0.03 in control subjects; P<0.001) and in those children whose mothers had premature CAD, EDD/EID index was markedly lower than control subjects, too (0.92 +/- 0.04 versus 1+/- 0.03; P< 0.001). ANOVA of these positive family history subgroups showed statistical significance (F = 26.12, P< 0.001), but in pairwise analysis EDD/EID index in subgroups of father or mother with CAD was not significantly different.

On Pearson Correlation analysis of the combined group of 30 positive family history subjects and control subjects, there was direct correlation between BBD and age (r = 0.63, P <0 .001), but EDD/EID was inversely related to age (r = - 0.21, P<0.05).

Table 3. Noninvasivse Brachial artery evaluation results.

	Premature CAD Group				Control Group				t-test	
	Mean	SD	Min	Max	Mean	SD	Min	Max	t	P
BBD	3.62	0.5	2.2	5	3.58	0.5	2.8	4.4	0.33	0.36
EDD/BBD	8.5	3.4	0	0.14	11.8	4.5	0.02	0.22	9.98	0.003
EID/BBD	18.5	6.7	0.04	0.29	11.9	5.2	0.05	0.30	18.7	<0.001
EDD/EID	0.92	0.05	0.84	1.02	1	0.03	0.88	1.03	7.26	<0.001

BBD= Basal Brachial artery Diameter; EDD/BBD= Endothelium Dependent Dilatation;
EID/BBD= Endothelium Independent Dilatation; EDD/EID= Endothelium Dependent
Dilatation / Endothelium Independent Dilatation or index of endothelial Function.

Discussion

This study showed that offsprings of premature CAD patents have endothelial dysfunction. Endothelial dysfunction means EDD/EID index less than one.The less the EDD/EID index is, the more impairment of endothelial function is present. It showes that the amount of dilatation of artery in response to shear stress is lesser than its dilatation in response to GTN. Endothelial dysfunction was obvious in subjects without additional risk factors except family history of premature CAD. There is no difference whether father has premature CAD or mother, it means that if a man or a woman has premature CAD, his or her children are in risk of development of endothelial dysfunction and, eventually, establishment of CAD.

In a similar study in Australia by Clarkson PB et al it has been shown that young adults with a family history of premature coronary disease have impaired endothelium-dependent dilatation [17]. Although these results are the same as our study but their study was done in siblings of premature coronary disease patients, where as this study was on children of these patients and showed that even one parent with premature coronary disease has some risk for his or her children for development of endothelial dysfunction and perhaps CAD in future.

In a Swedish study by Lind L et al it was showed that apparently healthy subjects with a family history of myocardial infarction have impaired endothelial-dependent vasodilation in the forearm vasculature that was independent to traditional cardiovascular risk factors such as impairment of blood pressure, lipids, fasting blood glucose levels, smoking habits, or intima-thickness of the carotid artery compared with those without the history of MI [18].

In this study we excluded subjects with identifiable risk factors, ie, smoking, passive smoking, hypertension, diabetes, and dyslipidemia, because in previous studies, influence of these cardiovascular risk factors on arterial function has been demonstrated [17, 20-22]. Most of mechanisms responsible for regulation of vascular tone and function are unknown for us but one discovered is the role of renin-angiotensin-system [23]. There are many pharmacological and nonpharmacological interventions that improve or even normalize endothelial function in human: Low Cholesterol diet, fish oil consumption, smoking cessation, and exercise training are effective nonpharmacological interventions that their efficacy have proved in many trials [24]. Some pharmacological therapies are as followes: L-Arginine supplementation, lipid lowering agents, especially statins; inhibitors of renin-angiotensin-aldosteron system such as ACE inhibitors [24], and calcium channel blockers like Amlodipine [25].

When we identified those children with endothelial dysfunction, it suggests that they are at risk of CAD in future. By performing these interventions, known as primary prevention, we can be hopeful that they will not be at risk thereafter and it may reduce CAD incidence in future. We suggest Endothelial function evaluation in offsprings of premature CAD parents and if it is abnormal, interventions known as primary prevention for them.

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