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Original Article

The thickness of the intimal and medial layers of the carotid arteries, and the index of left ventricular mass, in children of patients with premature coronary arterial disease

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Abstract *Objective:* To compare the thickness of the intimal and medial layers of the carotid arteries, and the index of left ventricular mass, in children of parents suffering premature myocardial infarction, and to compare the findings with suitable controls. *Methods:* Our population comprised 112 healthy adolescents, aged from 12 to 18 years, with a parental history of onset of coronary arterial disease under 55 years of age. We compared this cohort with 127 adolescents matched for age and gender, but without any history of coronary arterial disease in their first and second relatives. The thickness of the carotid arterial layers, and left ventricular mass, were assessed by high resolution carotid ultrasonography and echo doppler examination, respectively. *Results:* The mean age, body mass index, systolic and diastolic blood pressures of the patients and their controls was not significantly different. The intimal and medial thicknesses, and the index of left ventricular mass, however, as well as the levels of total and low density lipoprotein cholesterol, were significantly higher in the group of patients. In the entire population studied, the levels of total and low density lipoprotein-cholesterol correlated significantly with the arterial mural thicknesses, whereas age, male gender, positive parental history of premature coronary arterial disease, low density lipoprotein-cholesterol, and the index of body mass had significant correlations with the index of left ventricular mass. After adjustment for all covariates, the association of parental history of premature coronary arterial disease with intimal and media thickness and the index of left ventricular mass remained significant ($R^2 = 0.3$). *Conclusion:* Our findings complement some recent observations of functional and structural changes in the arteries of young and older adults with a familial predisposition to coronary arterial disease, and emphasize the importance of primary prevention of such disease.

Keywords: Cardiovascular findings; paediatrics; arteriosclerosis; risk factors

The familial aggregation of coronary arterial disease is well documented. The specific underlying mechanisms, and the relative contribution of atherosclerosis to the subsequent coronary arterial events in subjects with a positive family history, however, are not well established.[1]

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Many case-control[2–5] and longitudinal[6–9] studies have revealed a familial pattern for coronary arterial disease. Given that the classic risk factors could account only for some, but not all, of the clustering of such disease in families, the inherited susceptibility, and/or environmental exposures, could explain this phenomenon. Some angiographic studies[10–12] demonstrated that patients with a positive family history had more advanced atherosclerotic occlusions and a larger number of affected coronary arteries, but other studies did not confirm this finding.[13]

Still other studies have shown a greater thickening of the coronary arteries in infants and children whose grandparents originated from geographic areas with a high incidence of coronary arterial disease than in other children.[14,15] Autopsy studies have also shown that intimal thickening of the coronary arteries in infancy is associated with a history of coronary arterial disease in the grandparents.[16]

The development of non-invasive methods, such as high resolution ultrasonography, now permits clinical assessment of abnormalities in vascular structure and function.[1,17,18] In our previous studies, we found higher levels of some classic and new risk factors, as well as immunologic factors and trace elements, in children with a parental history of premature coronary arterial disease.[19–22] In this study, we aimed to assess the thickness of the intimal and medial layers of the carotid arteries, and the index of left ventricular mass, in children of parents suffering premature myocardial infarction. Our findings will complement some recent observations of changes in arterial function and structure in adolescents with a familial predisposition to coronary arterial disease.

Methods

We studied 112 healthy adolescents, aged from 12 to 18 years, whose parents suffered premature coronary arterial disease under the age of 55 years.[23] The cohort was recruited consecutively from offspring of patients hospitalized for premature myocardial infarction between November, 2004, and March, 2006, at hospitals affiliated to Isfahan University of Medical Sciences in Iran. We recruited 127 subjects matched for age and gender, without any family history of coronary arterial disease in the first and second relatives, to serve as controls. In order to reduce the socio-demographic differences between the two groups, the controls were selected from offspring of families living in the same neighborhood as the group of cases.

The protocol was approved by the Ethics Committee of Isfahan Cardiovascular Center, which is approved by the National Institute of Health, United States of America. Written informed consent was obtained from the parents.

All subjects were invited to the Department of Preventive Pediatric Cardiology at Isfahan Cardiovascular Center. Physical examination was conducted by a team of trained physicians and nurses under the supervision of the same paediatrician. We calculated age from birth until the date of interview. Weight and height were measured with the subjects lightly clothed and barefoot, and recorded to the nearest 0.5 centimetre and 0.1 kilogram, respectively. Based on the recommendations of Lohman et al.,[24] we made 3 measurements of height and weight, using their average to compute the index of body mass as weight in kilograms divided by height in metres squared. These values were then converted to centiles using the reference data complied by the Center for Disease Control.[25]

Blood pressure was measured in a calm situation using mercury sphygmomanometers after at least 5 minutes of rest with the subjects sitting, the heart, cuff, and zero-indicator on the manometer all being at the level of the eye of the observer, who was a physician. All readings were taken in duplicate from the right arm. Cuffs of appropriate size were used, the width being 40% of the circumference of the upper arm, and the bladders of the cuffs covering from 80% to 100% of the circumference, and approximately two thirds of the length of the upper arm without overlapping. The procedure was explained to the students, and the cuff inflated and deflated once. The first measurement was not used in the analysis of this study. The reading at the first and the fifth Korotkoff phases were taken as systolic and diastolic blood pressures, respectively. The average of the two time measurements was recorded and included in the analysis. Elevated blood pressure was defined as the mean systolic and or diastolic blood pressure above the 90th percentile for that age and gender, after adjusting for weight and height.[26] Brachial pulse pressure was calculated as the difference between systolic and diastolic blood pressures.

For blood sampling, participants were instructed to fast for 12 hours. Compliance with fasting was determined by interview on the morning of examination. Ensuring the presence of one of the parents, samples were drawn from the ante-cubital veins of the adolescents between the hours of 8:00 and 9:00 in the morning. The samples were centrifuged for 10 minutes at 3000 revolutions per minute within 30 minutes of venipuncture, and were examined in the central laboratory of Isfahan Cardiovascular Research Center, which meets the national standards, and is also under the quality control of the Center for Disease Control of the United States of America, and the Department of Epidemiology, St. Rafael University, Leuven, Belgium. Fasting levels of blood sugar, triglycerides, and total and high density lipoprotein cholesterol were measured by an enzymatic method using an auto-analyzer (Hitachi, Model 902, Japan). High density lipoprotein cholesterol was determined after precipitation with dextran sulphate and magnesium of non-high density lipoprotein cholesterol.[27] Low-density lipoprotein cholesterol was calculated using

samples of serum with triglycerides less than or equal to 400 mg/dL according to the Friedewald equation.[28]

High resolution carotid ultrasonographic studies were performed with a Ving Med 750 machine, using a 7.5 MHz transducer for vascular and 3.5 MHz transducer for cardiac study. The images were recorded on videotape using a super VHS recorder and analyzed offline. An expert paediatric cardiologist, who was unaware of the family history, made all measurements. The protocol involved scanning of the posterior walls of the right and left common carotid arteries in their distal 1 centimetre. The crest at the origin of the bifurcation was used as an anatomical landmark to identify the segment to be visualized. In each examination, the cardiologist used different scanning angles to record the greatest thickness of the intimal and medial layers. On a longitudinal B-mode image, the posterior wall of the common carotid artery appears as two bright, parallel lines separated by a hypoechoic space. The inner line arises from the interface of the intimal layer with the lumen, whereas the outer line arises from the interface between the medial and adventitial layers. The distance between the interfaces represents the combined thickness of the intimal and medial layers.[29] For the purpose of measurement, the reader selected the three frames on each side that contained the thickest walls in the distal segment of the common carotid artery. The measurements were the averaged in order to give the mean mural thickness for each side.

The echo Doppler examination included a complete cross-sectional echocardiographic imaging, and an accurate Doppler interrogation, of all the cardiac chambers to exclude abnormalities of left ventricular wall motion, and any significant valvar lesions. All echocardiographic measurements, which were done by the same paediatric cardiologist, were reported as the average of at least three cardiac cycles, according to the criterions of the American Society of Echocardiography.

The index of left ventricular mass was obtained using M-mode echocardiography in the parasternal long axis view. Left ventricular measurements were made at or just below the tips of the leaflets of the mitral valve as described by Devereux et al.[30] The left ventricular mass was calculated from the measurements, in centimetres, in the Penn convention by using the thickness of the ventricular septum, the left ventricular internal dimension, and the thickness of the posterior left ventricular wall, all in diastole, by the following regression equation:

Penn-cube left ventricular mass is equal to 1.04 [(interventricular septal thickness in diastole plus left ventricular internal dimension in diastole plus posterior left ventricular wall thickness in diastole)^3 minus left ventricular internal dimension in diastole^3] – 13.6 grams. As correcting left ventricular mass for height^{2,7} minimizes the effect of gender, race, age, and obesity, the index of left ventricular mass was calculated as left ventricular mass divided by height in meters.[2,7,31]

Statistical analysis

Data were analyzed by the SPSS software package (SPSS, version 13.0, Inc. Chicago, IL). The sex-adjusted differences in mean value of the quantitative variables according to parental history of premature coronary arterial diseases were determined using Student's t test. The correlates for the combined intimal and media thickness, and the index of left ventricular mass, were studied by multiple regression analyses conducted once for the entire participants, and once for those with or without positive parental history of premature coronary arterial disease, separately. The association of having a positive parental history of premature coronary arterial disease with arterial mural thickness and index of left ventricular mass in the entire population under study was assessed after adjusting for all covariates. Pearson correlation coefficients were determined for the bivariate associations of arterial mural thickness and index of left ventricular mass with the variables assessed. The level of significance was set at a value for p of less than 0.05.

Results

The mean age, index of body mass, fasting blood sugar, triglycerides, high density lipoprotein-cholesterol, and systolic and diastolic blood pressures were not significantly different between the cases and their controls. The combined carotid intimal and medial thickness, the left ventricular mass, the index of left ventricular mass, and the total and low density lipoprotein cholesterol were significantly higher in the cases than in their controls (Table 1).

The multiple regression analysis conducted among the entire population showed that having a positive parental history of premature coronary arterial disease, as well as the levels of total and low density lipoprotein cholesterol, were significantly correlated with the combined carotid arterial intimal and medial thicknesses, whereas age, male gender, positive parental history of premature coronary arterial disease, low density lipoprotein cholesterol, and the index of body mass, all had significant correlations with the index of left ventricular mass. Systolic and diastolic blood pressures, as well as brachial pulse pressures, had

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Table 1. Sex-adjusted cardiovascular risk factors according to parental history of premature coronary arterial disease.

	Parental History of premature coronary arterial disease		
	Negative (n = 127) Mean plus/minus standard error (standard deviation)	Positive (n = 112) Mean plus/minus standard error (standard deviation)	p
Male (%)	58	55.4	0.7
Age (years)	14.7 ± 0.2 (2.2)	15.3 ± 0.2 (2.3)	0.09
Carotid mural thickness (mm)	0.22 ± 0.007 (0.05)	0.29 ± 0.008 (0.07)	0.02
Left ventricular mass (gr)	107.2 ± 14.2 (10.1)	116.01 ± 18.2 (15.2)	0.03
Index of left ventricular mass ($gr/m^{2.7}$)	36.2 ± 11.2 (10.4)	37.8 ± 12.1 (10.9)	0.02
Index of body mass (kg/m^2)	22.2 ± 0.7 (6.8)	21.2 ± 0.5 (5.3)	0.3
Systolic blood pressure (mmHg)	103.7 ± 1.3 (11.6)	104.1 ± 0.9 (9.6)	0.8
Diastolic blood pressure (mmHg)	69.4 ± 1.2 (10.4)	70.4 ± 1.01 (10.07)	0.5
Brachial pulse pressure (mmHg)	41.2 ± 1.7 (2.7)	40.8 ± 1.6 (2.1)	0.6
Fasting blood sugar (mg/dL)	85.4 ± 7.2 (10.2)	86.1 ± 6.4 (11.4)	0.6
Total cholesterol (mg/dL)	170.01 ± 2.9 (26.3)	176.1 ± 2.9 (30.9)	0.04
LDL-cholesterol (mg/dL)	105.8 ± 12.1 (25.9)	117.04 ± 12.6 (28.1)	0.02
HDL-cholesterol (mg/dL)	37.1 ± 1.8 (5.7)	34.5 ± 1.2 (5.1)	0.5
Triglycerides (mg/dL)	148.1 ± 12.8 (21.7)	142.4 ± 12.5 (22.1)	0.4

Table 2. Characteristics of all participants, and multiple regression analysis of variables with carotid mural thickness and index of left ventricular mass.

		Regression coefficients (standard error)	
Variable	Mean (standard deviation)	Correlation with carotid mural thickness	Correlation with index of left ventricular mass
Age (years) mean (standard deviation)	14.9 (2.3)	0.04 (0.003)	0.2 (0.007)*
Index of body mass (kg/m^2) mean (standard deviation)	21.3 (6.8)	0.1 (0.01)	0.3 (0.02)*
Systolic blood pressure (mmHg) mean (standard deviation)	103.4 (10.01)	0.01 (0.002)	0.04 (0.001)
Diastolic blood pressure (mmHg) mean (standard deviation)	69.4 (9.6)	0.1 (0.001)	0.2 (0.06)
Brachial pulse pressure (mmHg) mean (standard deviation)	40.2 (1.8)	0.1 (0.001)	0.1 (0.002)
Fasting blood sugar (mg/dL) mean (standard deviation)	85.7 (6.8)	0.01 (0.001)	0.02 (0.001)
Total cholesterol (mg/dL) mean (standard deviation)	171.5 (26.5)	0.2 (0.01)*	0.1 (0.03)
Low density lipoprotein-cholesterol (mg/dL) mean (standard deviation)	104.5 (25.1)	0.3 (0.001)*	0.4 (0.02)*
High-density lipoprotein cholesterol (mg/dL) mean (standard deviation)	35.2 (1.1)	0.01 (0.001)	0.1 (0.004)
Triglycerides (mg/dL) mean (standard deviation)	144.1 (21.1)	0.1 (0.01)	0.1 (0.001)
Prevalence (%)			
Male (%)	55.3	0.1 (0.01)	0.2 (0.07)
Positive parental history of premature coronary arterial disease (%)	53.1	0.3 (0.001)*	0.3 (0.02)*

*$p < 0.05$ for correlations.

no correlation either with the combined carotid arterial intimal and medial thicknesses, nor with the index of left ventricular mass (Table 2).

After adjustment for all covariates, namely age, sex, index of body mass, blood pressure, and biochemical variables, the association of having a positive parental history and the combined carotid arterial mural thickness and the index of left ventricular mass remained significant ($R^2 = 0.3$).

Multiple regression analysis conducted separately for those with or without a positive parental history of coronary arterial disease showed that, in the subjects, but not their controls, low density lipoprotein cholesterol and the index of body mass were the only two factors associated with the carotid arterial mural thickness, but age, index of body mass, and systolic blood pressure had significant associations with the index of left ventricular mass.

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Table 3. Multiple regression analysis of variables associated with carotid mural thickness and index of left ventricular mass in the cases and their controls.

	Parental history of premature coronary arterial disease			
	Positive		Negative	
	Regression coefficient (standard error)		Regression coefficient (standard error)	
Variables	Carotid mural thickness	Index of left ventricular mass	Carotid mural thickness	Index of left ventricular mass
Age (years)	0.1 (0.02)	0.2 (0.02)*	0.1 (0.004)	0.2 (0.006)*
Male (%)	0.1 (0.01)	0.1 (0.0.5)	0.2 (0.01)	0.1 (0.005)
Index of body mass (kg/m^2)	0.3 (0.01)*	0.3 (0.002)*	0.2 (0.04)	0.1 (0.02)
Systolic blood pressure (mmHg)	0.1 (0.001)	0.2 (0.05)*	0.1 (0.001)	0.2 (0.1)
Diastolic blood pressure (mmHg)	0.1 (0.001)	0.1 (0.005)	0.1 (0.02)	0.1 (0.05)
Brachial pulse pressure (mmHg)	0.1 (0.001)	0.1 (0.002)	0.1 (0.01)	0.1 (0.02)
Fasting blood sugar (mg/dL)	0.01 (0.001)	0.02 (0.001)	0.01 (0.004)	0.05 (0.001)
Total cholesterol (mg/dL)	0.2 (0.07)	0.1 (0.001)	0.1 (0.001)	0.1 (0.01)
LDL-cholesterol (mg/dL)	0.4 (0.02)*	0.1 (0.004)	0.2 (0.01)*	0.1 (0.004)
HDL-cholesterol (mg/dL)	0.1 (0.002)	0.2 (0.07)	0.1 (0.01)	0.1 (0.002)
Triglycerides (mg/dL)	0.1 (0.004)	0.2 (0.001)	0.1 (0.004)	0.1 (001)

*$p < 0.05$ for correlations.

In the controls, low density lipoprotein cholesterol was associated with the carotid arterial mural thickness, whereas age was associated with the index of left ventricular mass (Table 3).

In Table 4, we show the Pearson correlations of the variables assessed with carotid arterial mural thickness and the index of left ventricular mass in the cases and their controls, as well as in the total population studied. In the cases, total and low density lipoprotein cholesterol, as well as systolic blood pressure, was significantly correlated with the carotid arterial mural thickness. In this group, age, index of body mass, low density lipoprotein cholesterol, and systolic blood pressure correlated with the index of left ventricular mass. In the controls, we found that age, as well as total and low density lipoprotein cholesterol, correlated with the arterial mural thickness, whereas age and systolic blood pressure correlated significantly with the index of left ventricular mass. In the total population studied, it emerged that age, systolic blood pressure, and total and low density lipoprotein cholesterol all correlated with the mural thickness of the carotid arteries, whilst systolic blood pressure correlated with the index of left ventricular mass.

Discussion

Our findings show that, compared to controls, our adolescents with a family history of premature coronary arterial disease have higher degrees of subclinical atherosclerosis and left ventricular hypertrophy. The levels of total and low density lipoprotein cholesterol in the serum were correlated with these abnormal cardiovascular findings, but after adjustment for all covariates, we found an independent association of positive parental history of premature coronary arterial disease with an increased mural thickness of the carotid arteries and the index of left ventricular mass.

There are few previous studies that have assessed the relationship between measurements of atherosclerosis in the carotid arteries and a family history of coronary arterial disease, and the few studies conducted among adults remain controversial. In the Cardiovascular Health Study, it was shown that an increased carotid arterial mural thickness in elderly subjects was associated with family history of premature myocardial infarction in first degree relatives.[32] In a Finnish study,[33] in contrast, the severity of carotid atherosclerosis was not proven to be associated with family history of coronary arterial disease. In the study of Zureik and colleagues,[1] also involving an elderly population, although parental history of premature death from coronary arterial disease was strongly associated with presence of plaques in the carotid arteries, it was not associated with an increased arterial mural thickness. These authors suggested that familial transmission of the risk of coronary arterial disease is not mediated specifically by arterial mural thickening when measured at sites free of plaques.[1]

Some studies, nonetheless, have shown that risk factors identified in childhood are independent predictors of an increased mural thickening of the

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Table 4. Pearson correlation of variables with carotid mural thickness and index of left ventricular mass with or without parental history of premature coronary arterial disease.

	Carotid mural thickness		Index of left ventricular mass		Carotid mural thickness	Index of left ventricular mass
	Parental premature coronary arterial disease		Parental premature coronary arterial disease		All	All
	Positive r	Negative r	Positive r	Negative r	r	r
Age (years)	0.1	0.3*	0.3*	0.3*	0.2*	0.02
Index of body mass (kg/m^2)	0.1	0.03	0.2*	0.1	0.1	0.1
Fasting blood sugar (mg/dL)	0.07	0.05	0.08	0.06	0.05	0.04
Total cholesterol (mg/dL)	0.3*	0.2*	0.1	0.09	0.2*	0.1
LDL-cholesterol (mg/dL)	0.4**	0.2*	0.3*	0.2	0.3*	0.1
HDL-cholesterol (mg/dL)	0.1	0.08	0.09	0.07	0.07	0.09
Triglycerides (mg/dL)	0.1	0.1	0.1	0.08	0.09	0.08
Systolic blood pressure (mmHg)	0.2**	0.03	0.4**	0.3*	0.2*	0.2*
Diastolic blood pressure (mmHg)	0.05	0.07	0.06	0.09	0.06	0.07
Brachial pulse pressure (mmHg)	0.04	0.02	0.05	0.04	0.02	0.05

*$p < 0.05$; **$p < 0.0001$.

carotid arteries in adulthood,[33–36] suggesting that exposure to risk factors in childhood may induce permanent effects on arteries that contribute to the development of future atherosclerosis.[34,37] Cuomo et al.[38] showed that the thickness of the carotid arteries in healthy young subjects aged from 5 to 30 years, with a parental history of premature coronary arterial disease, was higher than in controls.

Several investigations have concluded that screening the progeny of patients suffering from early incidence of atherosclerotic events is highly productive in the identification of those at an increased risk for future coronary arterial disease.[23] Differences in the geographic and ethnic predisposition to coronary arterial disease are well documented in different populations.[39] As far as we are aware, ours is the first study of its kind performed in a non-Western population of youths. It confirms that subjects genetically predisposed to early coronary arterial disease have higher degrees of subclinical atherosclerosis, even from adolescence.

Some previous longitudinal studies have documented the role of childhood cardiovascular risk factors, notably high levels of low density lipoprotein cholesterol, in predicting increased carotid arterial mural thickness in adulthood.[34–35] Although our previous national study showed that, in population-based studies, the usefulness of family history of premature cardiovascular disease is relatively low in identifying dyslipidaemic children,[40] this study is consistent with our previous studies on children of known cases of coronary arterial disease[19–22] in showing that levels of total and low density lipoprotein cholesterol in the serum were higher in those adolescents with a parental history of premature coronary arterial disease. In addition, we found a significant association between the level of low density lipoprotein cholesterol in the serum and the arterial mural thickness. This correlation is well established among young adults.[41–42]

Increased left ventricular mass is an independent risk factor for cardiovascular morbidity and mortality.[43] Given that subjects with increased left ventricular mass might be at high risk of developing coronary arterial disease, and that a family history of premature coronary arterial disease is a well-established risk factor for subsequent coronary arterial disease in the subject, our other goal was to compare the left ventricular mass of youths with and without such family history, as well as the association between the family history of premature coronary arterial disease and the left ventricular mass. We found a higher index of left ventricular mass in the children of patients with premature myocardial infarction than in their controls, this being contrary to the study of Dekkers et al.[44] We also showed that a family history of premature myocardial infarction was significantly correlated with left ventricular mass, this association remaining significant even after adjustment for blood pressure and body mass index. The strength of the study of Dekkers et al.[44] is its longitudinal nature, but it has been subject to recall bias concerning the premature coronary arterial disease in the relatives. Our study, although cross-sectional, was conducted among children of known parents suffering

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premature myocardial infarction, and is therefore more reliable in this regard.

We found significant correlations between the indexes of body mass and left ventricular mass. Linear growth is known as the major determinant of cardiac growth in children, and it is also known that excess weight may lead to the acquisition of left ventricular mass beyond that expected from normal growth. Increased mass may also precede the development of increased blood pressure.[45] Considering that findings of longitudinal studies have shown that obesity beginning in childhood is one of the significant predictors of left ventricular hypertrophy in an otherwise healthy population of young adults,[46] the importance of implementation of preventive measures against childhood obesity should be emphasized in clinical settings, and in programmes designed to improve public health.

We should acknowledge that certain factors might have influenced the findings of the present study. Its major limitation is that the correlations should be interpreted with caution, given the cross-sectional nature of the associations. Longitudinal and genetic studies would help the understanding of the differences in susceptibility of developing early atherosclerosis.

In conclusion, our findings complement some recent observations of functional and structural changes in the systemic arteries of young and older adults with a familial predisposition to coronary arterial disease. They emphasize the importance of seeking to prevent coronary arterial disease in primary fashion, especially using the recommended high risk approach, amongst those children known to be susceptible to such future disease.

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