The relation between aortic atherosclerosis and risk factors

Aort aterosklerozu ile risk faktörleri arasındaki ilişki

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ABSTRACT

Objective: To evaluate the impact of risk factors on atherosclerotic changes of aortic wall and valve in patients with and without non-familial hypercholesterolemia by transthoracic echocardiography.

Methods: One hundred and eleven patients with non-familial hypercholesterolemia and 112 control subjects were included in the study. Aortic wall and valve were evaluated by visual assessment of wall hyperechogenicity and measuring the valve thickness. Aortic diameters were obtained at the levels of annulus, sinus of Valsalva and at the supravalvular level in the parasternal long-axis view by M-Mode echocardiographic examination. The relationship between parameters of aortic atherosclerosis and risk factors was studied by multivariate logistic regression analysis, Pearson and Spearman correlation analyses.

Results: The prevalence of aortic wall hyperechogenicity was found to be higher in patients with hypercholesterolemia (84.7% vs 70.5%, p=0.01). The mean aortic root diameters at all levels of patients with hypercholesterolemia were found to be significantly smaller than in patients of the control group (3.1±0.3 mm vs 3.2±0.5 mm, p=0.02 for annulus level, 3.4±0.4 mm vs 3.5±0.4, p=0.004 mm for the level of sinus of Valsalva and 3.2±0.3 mm vs 3.4±0.5 mm, p<0.001 – supravalvular level), but no difference was noted regarding the aortic velocity and pressure gradient across the aortic valve. Multivariate stepwise logistic regression analysis showed that age (OR=1.1, CI – 1.02-1.09, p=0.002) and smoking (OR=2.2, CI – 1.06-4.58, p=0.04) were independent predictors of aortic valve thickness. Hypercholesterolemia was an independent predictor for aortic wall hyperechogenicity (OR=2.5, CI – 1.3-4.9, p=0.009) but not for valve thickness.

Conclusions: Age, smoking and hypercholesterolemia are related to atherosclerotic involvement of aortic wall and valve. *(Anadolu Kardiyol Derg 2007; 7: 2-5)*

Key words: Aortic atherosclerosis, risk factors, transthoracic echocardiography, regression analysis

ÖZET

Amaç: Ailevi olmayan hiperkolesterolemili hastalarda risk faktörlerinin aort duvarı ve kapağındaki aterosklerotik değişikliklere etkisinin transtorasik ekokardiyografi ile değerlendirilmesi.

Yöntemler: Çalışmaya hiperkolesterolemisi olan 111 hasta ile kolesterol düzeyleri normal bulunan 112 birey alındı. Aort duvarı ve kapağının hiperekojenitesi görsel olarak değerlendirildi. Aort yapraklarının kalınlığı ölçüldü. Aort çapları parasternal uzun eksende M-mod ekokardiyografi ile annulus, sinüs Valsalva ve supravalvüler düzeylerde kaydedildi. Aort aterosklerozu ile risk faktörleri arasındaki ilişki Pearson ve Spearman ile çok değişkenli regresyon analizi ile değerlendirildi.

Bulgular: Aort kapak hiperekojenitesi sıklığı hiperkolesterolemili hastalarda kontrollere göre daha yüksek bulundu (%84.7 ve %70.5, p=0.01). Hasta grubunda tüm kesitlerden ölçülen ortalama aort çapı daha küçük bulunmasına rağmen (annulusta: 3.1±0.3 mm ve 3.2±0.5 mm, p=0.02, sinüs Valsalva düzeyinde: 3.4±0.4 mm ve 3.5±0.4, p=0.004 ve supravalvüler düzeyde: 3.2±0.3 mm ve 3.4±0.5 mm, p<0.001), kapak gradiyenti ve kan akım hızı kontrol grubu ile benzer bulundu. Çoklu regresyon analizi ile yaş (OR=1.1, CI – 1.02-1.09, p=0.002) ve sigaranın (OR=2.2, CI – 1.06-4.58, p=0.04) aort kapak kalınlığı için bağımsız birer gösterge olduğu saptandı. Ayrıca hiperkolesterolemi aort kapak hiperokojenitesi için bağımsız bir gösterge (OR=2.5, CI – 1.3-4.9, p=0.009) olarak bulunmasına rağmen kapak kalınlığı ile ilişkili bulunmadı.

Sonuç: Yaş, sigara ve hiperkolesterolemi aort duvarı ile kapağındaki aterosklerotik tutulum ile ilişkilidir. *(Anadolu Kardiyol Derg 2007; 7: 2-5)*

Anahtar kelimeler: Aort aterosklerozu, risk faktörleri, transtorasik ekokardiyografi, regresyon analiz

Introduction

Atherosclerotic involvement of the aorta is associated with increased risk of cardiovascular events and ischemic stroke (1-3). It is known that several clinical and laboratory parameters are related to aortic atherosclerosis (4-7). One of these factors is hyperlipidemia. It is reported that aortic atherosclerosis is often present in patients with homozygous familial hyperlipidemia, but its incidence is rare in heterozygous patients (8). The majority of studies on this issue involve the evaluation of thoracic atherosclerosis by transesophageal echocardiography (6-7). The aim of this study is to evaluate the effect of risk factors on atherosclerotic changes of aortic wall and valve in patients with and without non-familial hypercholesterolemia by transthoracic echocardiography (TTE).

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Methods

Patients: Two hundred and twenty three patients who underwent coronary angiography due to suspicion of coronary artery disease were selected randomly for this study. Hypercholesterolemia was defined as plasma total cholesterol level ≥200 mg/dl and/or low density lipoprotein (LDL)-cholesterol level ≥130 mg/dl (9). Age, gender, familial history for coronary artery disease, smoking, hypertension and diabetes mellitus were considered as risk factors. A positive family history was defined as coronary artery disease in a parent or sibling noted under the age of 55 for men and 65 for women. A sustained blood pressure greater than 140 mmHg systolic and 90 mmHg diastolic or using antihypertensive drugs at the time of investigation was defined as hypertension. Diabetes mellitus was considered to be present if there was a history of diabetes, fasting blood glucose ≥126 mg/dL or the use of an antidiabetic medication (10). Body mass index was calculated as weight (kg)/height $(m)^2$.

Echocardiography: Transthoracic echocardiography was performed in all patients by using Acuson Sequoia C 256 equipment (Acuson Corp, Mountain View, California, USA). Complete two-dimensional and Doppler examinations were obtained with a 3.5 MHz transducer. Aortic wall and valve were evaluated by visual assessment of the wall hyperechogenicity and measuring the valve thickness. Aortic hyperechogenicity was evaluated in the parasternal long-axis view and it was defined as normal or hyperechogenic according to the previously described method (8). Aortic valve leaflets were evaluated in the short-axis view and thickness was classified as being normal or abnormal. Aortic valve thickness was assessed by measuring the most thickened cusp at the maximum affected area. The leaflets were considered abnormal if there was either nodular calcification or ≤ 2 mm thickness, diffuse thickness (2-4 mm) and thickness more than 4 mm. Aortic diameters were obtained at the levels of annulus, sinus of Valsalva and at the supravalvular level in the parasternal long-axis view by M-Mode echocardiographic examination. Aortic velocity was determined in apical five-chamber imaging by continuous wave Doppler.

Statistical analysis: Statistical analysis was performed by using the SPSS for Windows 6.0 program. All values were expressed as mean ± standard deviation. Unpaired Student's t test was used for comparison of the quantitative variables. Chi-square test was also used for comparison of the qualitative variables. Relation between echocardiographic parameters and clinical findings were evaluated by Pearson (for continuous variables) and Spearman (for non-continuous variables) correlation analyses. Multivariate stepwise backward conditional logistic regression analysis was used to determine the relative importance of the independent predictors associated with aortic wall thickness and hyperechogenicity. P value <0.05 was considered statistically significant.

Results

The mean age of 223 patients (130 men, 93 women) was 54.4 ± 9.9 (range 35-80) years. Group 1 and Group 2 consisted of 111 and 112 patients, respectively. Family history (39.5%) and hypertension (37.6%) were recorded as the most common risk factors. Clinical and laboratory parameters of the patients are shown in Table 1. There was no significant difference between two groups regarding age, gender and atherosclerotic risk factors other than hypercholesterolemia. The prevalence of aortic wall hyperechogenicity was found to be significantly higher in patients with hypercholesterolemia (p=0.01). The mean aortic root diameters at all levels of patients with hypercholesterolemia were found to be significantly smaller (p=0.02, p=0.004 and p=0.001 for annulus, sinus of Valsalva and supravalvular level respectively) than that of the control group, but no difference was noted regarding the aortic velocity and pressure gradient across the aortic valve (Table 2).

The clinical and echocardiographic findings of all patients in this study showed a significant correlation between the thickness of aortic valve and age and smoking. However no such relation was found between aortic wall hyperechogenicity and clinical risk factors other than hypercholesterolemia. Furthermore, logistic regression analysis showed that age (odds ratio, OR=1.1, p=0.002) and smoking (OR=2.2, p=0.04) were the independent predictors of aortic wall thickness and hypercholesterolemia was the sole predictor (OR=2.5, p=0.009) of aortic wall hyperechogenicity (Table 3).

In addition a significant negative correlation was found between total cholesterol and LDL-cholesterol levels and aortic root diameters in sinus of Valsalva and supravalvular cross-sections, respectively (p<0.03). A positive correlation was found between age, male gender and smoking and aortic diameters in annulus, sinus of Valsalva and supravalvular levels. Age, female gender and hypertension were found to be related to the mean transaortic gradient velocity. On the other hand, smoking was found to be inversely related to the mean transaortic gradient (Table 4).

Discussion

There are numerous clinical and biochemical risk factors which affect the atherosclerotic involvement of aortic wall and valve (5-7, 11-13). Generally accepted risk factors for aortic atherosclerosis include age, hypertension, family history, diabetes mellitus, smoking, and hyperlipidemia (4-7). However, the outco-

Table 1. Characteristics of the patients with and without hypercholesterolemia

Variables	Patients (n=111)	Controls (n=112)
Mean age, years	53.2 ±10.8	55.6 ±9.6
Gender, M/F	61/50	69/43
Family history, n (%)	47 (42.3)	41 (36.6)
Smoking, n (%)	35 (31.5)	34 (30.4)
Hypertension, n (%)	47 (42.3)	37 (33.0)
Diabetes mellitus, n (%)	16 (14.4)	19 (17.0)
Body mass index, kg/m^2	28.5±3.9	27.7±4.0
Total-cholesterol, mg/dl (range)	232.8±28.5 (200.0-344.0)	172.4±24.5*** (115.0-199.0)
LDL-cholesterol, mg/dl (range)	148.1±25.1 (130.0-235.0)	100.0±24.1*** (49.0-129.0)
HDL- cholesterol, mg/dl (range)	42.7±10.0 (23.0-97.0)	38.3±9.5** (23.0-65.0)
Triglycerides, mg/dl (range)	206.8±109.1 (57.0- 621.0)	175.8±98.5* (56.0-298.0)

Data presented are the number (%) of patients for categorical variables and Mean±standard deviation for continuous variables
*p<0.03; **p<0.001; ***p<0.0001
HDL- high density lipoprotein, LDL- low density lipoprotein, M/F- male/female

mes of studies investigating the independent risk factors do not necessarily overlap. For instance, Triboully et al (7) showed that age, smoking, diabetes mellitus and LDL-cholesterol level are the major independent risk factors while Agmon et al. (11) determined these as age, smoking and hypertension. These studies are based on evaluation of atherosclerotic involvement of thoracic aorta by transesophageal echocardiography (6, 7 11). Transesophageal echocardiography is a more sensitive tool but the potential risk and discomfort to the patient is higher with this relatively invasive approach. Aronow et al (5) showed that high total-cholesterol and low HDL-cholesterol levels, hypertension, and diabetes mellitus were related to aortic atherosclerosis by using of transthoracic echocardiography. In the Helsinki Aging Study (14) age, hypertension and low body mass index were shown to be independent predictors of aortic valve calcification while cholesterol, smoking and diabetes were not. On the other hand, Stewart et al. (4) reported that the risk factors for aortic atherosclerosis and coronary artery disease are essentially similar and age, male gender, hypertension, smoking and levels of LDL-cholesterol and lipoprotein (a) are independent predictors of aortic sclerosis and stenosis.

Table 2. Comparison of aortic wall and valve changes and Doppler findings in patients with and without hypercholesterolemia

Variables	Patients	Controls
Aortic hyperechogenicity, n (%)	94 (84.7)	79 (70.5) **
Thickness, n (%)	68 (61.3)	73 (65.2)
Annulus, mm	3.1±0.3	3.2±0.5*
Valsalva, mm	3.4±0.4	3.5±0.4***
Supravalvular, mm	3.2±0.3	3.4±0.5****
Gradient maximum, mmHg	7.4±8.5	9.5 ±12.4
Gradient mean, mmHg	4.0±4.0	5.3±7.4
Velocity maximum, m/s	1.7±4.1	1.4±0.6
Velocity mean, m/s	0.9±0.3	1.0±0.5

Data presented are the number (%) of patients for categorical variables and Mean±standard deviation for continuous variables
*p= 0.02; **p=0.01; ***p=0.004; ****p<0.001

Although atherosclerotic changes in aortic wall and valve are common findings in patients with homozygous familial hyperlipidemia, these changes are rare in heterozygous individuals (8). According to another study aortic valve was found to be frequently involved in patients with hyperlipidemia (15). In the present study we found that aortic hyperechogenicity was more frequent in patients with non-familial hypercholesterolemia when compared with the control group. Moreover, hypercholesterolemia was an independent predictor for aortic wall hyperechogenicity but not for valve thickness. On the other hand, age and smoking were the independent predictors for aortic valve thickness. We noted that the mean age of patients in our study was much lower in comparison to the studies which underline the role of plasma cholesterol levels, hypertension and other factors as independent predictors (5, 12, 13) Conversely, although the mean age of patients with familial hyperlipidemia (8) was much lower than of our patients, their mean cholesterol levels were significantly higher. Hence, these differences in age and cholesterol levels may account for the fact that in our study we found no significant difference in aortic valve thickness between patients with hypercholesterolemia and control subjects. Furthermore, the reported differences between results of these studies may be related to the characteristics of patients and duration of the risk factors.

Pitsavos et al (16) found that there was no difference in aortic root dimensions in patients with heterozygous familial hypercholesterolemia, when compared with normal subjects. But, these patients had abnormal elastic properties of the ascending aorta (16). In our study, we found that the aortic diameters at valvular, sinus of Valsalva, and supravalvular levels were smaller in patients with

Table 3. The independent predictors of atherosclerotic changes of aortic valve and wall - logistic regression analysis data

Variables	Odds ratio	CI (95%)	p
Age-AV thickness	1.1	1.02-1.09	0.002
Smoking- AV thickness	2.2	1.06-4.58	0.04
HC-hyperechogenicity	2.5	1.3-4.9	0.009

AV- aortic valve, HC- hypercholesterolemia, CI- confidence interval

Table 4. The relation between clinical and echocardiographic findings of all patients by correlation analysis

	Age, years	Gender	Smoking, n (%)	HT, n (%)	HC, n (%)
Hyperechogenicity, n (%)	*	*	*	*	r=0.17 p=0.01
Thickness, n (%)	r=0.18 p=0.006	*	r=0.15 p=0.03	*	*
Annulus, mm	r=0.15 p=0.03	r=0.38 p=0.001	r=0.31 p=0.001	*	r=-0.14 p=0.04
Valsalva, mm	r=0.15 p=0.02	r=0.44 p=0.001	r=0.26 p=0.001	*	r=-0.18 p=0.007
Supravalvular, mm	r=0.20 p=0.003	r=0.18 p=0.006	r=0.17 p=0.01	*	r=-0.20 p=0.003
Gradient, mmHg	r=0.14 p=0.03	r=0.34 p=0.001	r=0.17 p=0.01	r=0.15 p=0.03	*
Velocity, m/s	r=0.19 p=0.005	r=0.31 p=0.001	*	r=0.18 p=0.008	*

HT- hypertension, HC- hypercholesterolemia, *- not significant

hypercholesterolemia compared to the control group. A possible explanation for this finding might be the diminished elasticity of the aortic wall. As a matter of fact, this hypothesis is supported by the fact that there was a significant negative correlation between the total and LDL-cholesterol levels and aforementioned aortic diameters. The aortic diameters increased with age at all levels and a positive correlation was found between gender and the aortic diameters (17, 18). Smoking has been also suggested as a possible cause of deterioration of aortic elastic properties (19). In particular cadmium content of cigarette smoke reportedly impairs the viability of cultured smooth muscle cells (20). In support of these hypotheses, we found a positive correlation between age and smoking and aortic diameters at all levels of ascending aorta. We did not find relation between hypertension and aortic root diameters. Association between hypertension and aortic root dilatation is controversial (21-25). The Framingham Heart Study (21) showed that diastolic pressure was directly related to aortic diameter, whereas both systolic and pulse pressures were inversely related to aortic diameter after adjustment for age, height, and weight. Some echocardiographic studies have noted significant relation between systolic or diastolic blood pressure and aortic root diameters (22-23). A recent study showed that hypertension is associated with slight increase in aortic diameters especially supravalvular level and proximal ascending aorta (24). In the contrast, other echocardiographic studies have not found an association between hypertension and aortic root diameters (25-27).

Our study confirmed that there is a relation between hypercholesterolemia and the aortic hyperechogenicity as well as smaller aortic diameters in patients with non-familial hypercholesterolemia. The other factors which affect the aortic diameters are age, male gender and smoking.

Limitations

The number of the patients included in our study was not large. The duration of hypercholesterolemia could not be determined. In addition, no attempt was made to follow up the prospective echocardiographic changes and to evaluate the effect of lipid lowering therapy. We believe that there is a need for studies in different regions which include larger groups of patients and which determine the effects of lipid lowering and antihypertensive agents and reduction other risk factors on aortic valve and wall changes.

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