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Relation between aortic stiffness and extension of coronary artery disease

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Aim: To investigate the relation between aortic stiffness and the extension/severity of coronary artery disease (CAD).

Materials and methods: A consecutive 100 patients with suspicion of CAD who underwent elective coronary angiography were enrolled in this study. Of those patients determined as having CAD, 63 were classified as Group I (mean age: 62.1 ± 10.3 years; 47 male and 16 female). Group II included 37 patients with normal coronary arteries (mean age: 51.4 ± 10.8 years; 20 male and 17 female). Aortic flexibility (aortic distensibility and stiffness index) was evaluated by echocardiography after coronary angiography in all of the patients. Patient data were gathered in relation to age, sex, and atherosclerotic risk factors. Stenosis above 50% was accepted as severe CAD. The extension of coronary artery disease was determined using the Gensini score.

Results: The mean age (62.1 ± 10.3 and 51.4 ± 10.8, respectively) and the male/female rate in Group I were higher than in Group II ($P < 0.001$ and $P = 0.035$, respectively). The mean aortic stiffness in Group I was significantly increased compared to Group II (8.9 ± 5.1 mm and 6.1 ± 4.6 mm, respectively; $P = 0.001$), whereas the mean aortic distensibility in Group I was significantly lower than in Group II (23.4 ± 16.5 mm and 42.4 ± 27.1 mm, respectively; $P < 0.001$). The aortic stiffness index increased and distensibility decreased in correlation with age, coronary artery risk factors, and extension of CAD.

Conclusion: The aortic stiffness index increased and distensibility decreased in correlation with CAD extension and the number of affected coronary arteries.

Key words: Aortic stiffness, distensibility, coronary artery disease extension, Gensini score, coronary angiography

Koroner arter hastalığının yaygınlığı ile aortik stiffnes ilişkisi

Amaç: Bu araştırmada, koroner arter hastalığının yaygınlığı ve ciddiyeti ile aortun elastikiyet özellikleri arasındaki ilişki araştırıldı.

Yöntem ve gereç: Çalışmaya, koroner arter hastalığı (KAH) şüphesiyle elektif koroner anjiyografi yapılan ardışık yüz hasta alındı. Bunlardan KAH tespit edilen, yaş ortalamaları 62,1 ± 10,3 yıl olan 47 erkek, 16 kadın toplam 63 hasta grup 1 olarak alındı. Koroner arterleri normal ve yaş ortalamaları 51,4 ± 10,8 yıl olan 20 erkek, 17 kadın toplam 37 olgu grup 2 olarak alındı. Koroner anjiyografi sonrası tüm hastalara ekokardiyografi yapılarak aortun elastik özellikleri (aortik distensibilite ve stifness index) ölçüldü. Hastaların yaş, cinsiyet ve ateroskleroz risk faktörleri sorgulandı. Koroner anjiyografide % 50'den fazla darlık olması ciddi koroner arter hastalığı olarak kabul edildi. Koroner arter hastalığının yaygınlığı gensini skoru ile belirlendi.

Bulgular: Grup 1 deki hastaların yaş ortalamaları (62,1 ± 10,3 yıl) ve erkek cinsiyet oranı, grup 2'den (51,4 ± 10,8) daha fazla bulundu (sırasıyla $P < 0.001$, $P = 0.035$). Grup 1'in aortik stifnes ortalaması grup 2'ye göre anlamlı derecede

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artarken (sırasıyla, 8,9 ± 5,1 mm, 6,1 ± 4,6 mm, P = 0.001). aortik distensibilite ortalaması ise anlamlı derecede azalmış bulundu (sırasıyla, 23,4 ± 16,5 mm, 42,4 ± 27,1 mm, P < 0.001). İleri yaş, koroner arter hastalığı risk faktörleri ve koroner arter hastalığının yaygınlığı ile korele olarak aortik stifnes indeks artmakta, distensibilite azalmaktadır.

Sonuç: KAH'ın yaygınlığı ve tutulan koroner damar sayısı ile orantılı olarak aortik stifnesi artmakta, distensibilite ise azalmaktadır.

Anahtar sözcükler: Aortik stifness, distensibilite, koroner arter hastalığı yaygınlığı, gensini skoru, koroner anjiyografi

Introduction

The development and progression of atherosclerosis is important, especially in cardiovascular diseases. Atherosclerosis decreases the flexibility of large vessels and the vascular bed, and the decreased flexibility facilitates atherosclerotic development. Currently, it is possible to measure the flexibility change (aortic, arterial stiffness index, and distensibility) by noninvasive echocardiography (1-3). It is obvious that large vessels are exposed to "stiffness" caused by structural changes that occur with the effects of atherosclerosis and cardiovascular risk factors. These structural changes are observed not only in the middle-aged and elderly population but also in the young population at a subclinical level (4). In particularly, in large vessel stiffness studies, it has been found that this process has a direct effect on cardiovascular morbidity or mortality (5). Studies have demonstrated that advanced age, cardiovascular risk factors (6), hypertension, smoking, hypercholesterolemia (7-12), coronary artery disease (13,14), left ventricular systolic, and diastolic dysfunction (15) change aortic flexibility. Although studies investigating the relation between atherosclerotic risk factors and arterial stiffness are available, the objective relation between the extension of atherosclerosis and aortic stiffness has not been investigated sufficiently. The aim of this study was to investigate whether there is a direct relation between the extension of coronary artery disease (CAD) and aortic stiffness.

Materials and methods

Study population

A consecutive 100 patients with suspicion of CAD who underwent elective coronary angiography were enrolled in this study. Of those patients determined as having CAD, 63 were classified as Group I (mean age: 62.1 ± 10.3 years; 47 male and 16 female). Group II included 37 patients with normal coronary arteries (mean age: 51.4 ± 10.8 years; 20 male and 17 female). Patient data were gathered in relation to age, sex, and atherosclerotic risk factors. The main characteristics of the patients are shown in Table 1. Informed consent was obtained from all of the patients. This study was performed at our clinics in accordance with the principles stated in the Declaration of Helsinki and was approved by the local ethics committee.

Coronary angiography

Coronary angiography was performed by a standard judging technique using the Allura Xper FD10 (Philips, Amsterdam, Netherlands). Severe CAD was described as having more than 50% narrowness in at least 1 coronary artery. Patients were classified as having 1, 2, or 3 patent vessels. The extension of coronary atherosclerosis was calculated using the Gensini score (16).

Biochemical studies

Blood samples were collected from all of the patients after a fasting period of 12 h, and their glucose, urea, creatinine, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were measured.

Echocardiography measurements

After 15 min of rest, echocardiography measurements were performed with a standard technique using the Vingmed Vivid 3 with a 2.5-MHz probe (GE Medical System, Horten, Norway) in the left lateral position. All of the echocardiography measurements were performed in 3 consecutive cycles and their average was calculated. The M-mode was recorded at 100 mm/s. According to the recommendation of the American Echocardiography Association, the M-mode measurements (left ventricle diastolic and systolic diameters, and left atrium systolic diameter) were obtained from the image of the parasternal long

axis (17). Traces obtained after placing the M-mode stick distally on a 3-cm aortic valve region were used to calculate the aorta systolic and diastolic diameters (18). While the systolic diameter was measured from the peak of the aortic trace, the diastolic diameter was obtained from the R peak of the ECG. Aortic distensibility was calculated as shown in Figure 1.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 for Windows. Descriptive statistic results were presented as mean, standard deviation, median, minimum, and maximum or as number and percentage for numeric and categorical parameters, respectively. The difference between the groups for categorical parameters was determined using Pearson's chi-square test. According to the distribution, the difference between the groups for numeric parameters was determined using Student's t-test or the Mann-Whitney U test. Correlation between the numeric parameters was presented using Spearman's correlation. Regression analysis was used for parameters assumed to affect the aortic stiffness index and distensibility. The significance level was assumed as $P < 0.05$.

$$\text{Distensibility} = \frac{A_s - A_d}{A_d \cdot (P_s - P_d) \cdot 1333} \cdot 10^7 \ (kPa^{-1} \cdot 10^{-3})$$

$$\text{Stiffness index} = \frac{\ln (P_s / P_d)}{(D_s - D_d) / D_d} \ (\text{Dimensionless}).$$

Figure 1. Aortic distensibility and stiffness index formulas.

Results

The mean age (62.1 ± 10.3 and 51.4 ± 10.8 years, respectively) and male/female rate in Group I were higher than in Group II ($P < 0.001$ and $P = 0.035$, respectively). The mean aortic stiffness in Group I was significantly increased compared to Group II (8.9 ± 5.1 mm and 6.1 ± 4.6 mm, respectively; $P = 0.001$), whereas the mean aortic distensibility in Group I was significantly lower than in Group II (23.4 ± 16.5 mm and 42.4 ± 27.1 mm, respectively; $P < 0.001$) (Figures 2 and 3). Coronary angiography results showed that

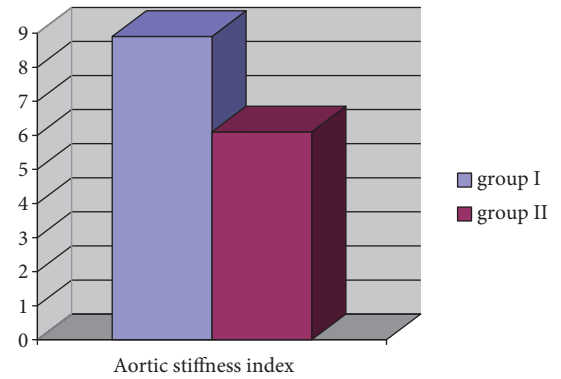

Figure 2. Aortic stiffness index in patient groups.

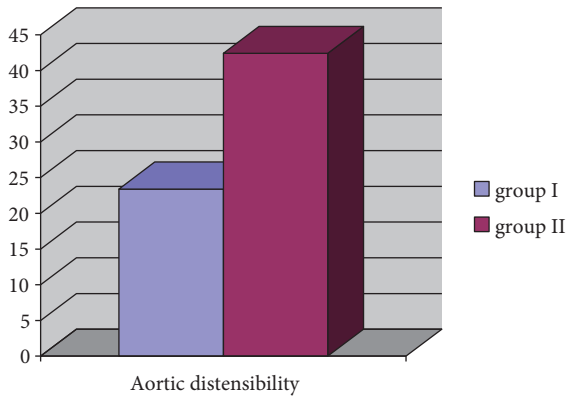

Figure 3. Aortic distensibility in patient groups.

the mean number of vessels with severe lesions and the Gensini score, which reflects CAD extension, was 2.2 ± 0.9 and 25.2 ± 31.0 (median: 14.0) in Group I, respectively.

In Group I, the mean values of hyperlipidemia and systolic and diastolic blood pressure (BP) were significantly higher than in Group II ($P = 0.011$, $P = 0.013$, and $P = 0.012$, respectively; Table 1).

In Group I, while the mean values of the left ventricular systolic (LVS) diameter, left atrial (LA) diameter, aortic diastolic field, aortic diastolic diameter, and aortic systolic diameter were significantly higher, the mean ejection fraction (EF) was significantly lower than in Group II ($P = 0.001$, $P = 0.005$, $P = 0.011$, $P = 0.007$, $P < 0.001$, and $P < 0.001$, respectively; Table 2).

While the aortic stiffness index had a positive correlation with the aortic diastolic and systolic

Table 1. Patient demographics.

	Group 1 (n = 63)	Group 2 (n = 37)	P-value
Age (years)	62.1 ± 10.3	51.4 ± 10.8	<0.001
Sex			0.035
Female, n (%)	16 (48.5)	17 (51.5)	
Male, n (%)	47 (70.1)	20 (29.9)	
Dyslipidemia			0.011
No, n (%)	21 (48.8)	22 (51.2)	
Yes, n (%)	42 (73.7)	15 (26.3)	
Smoking			0.728
No, n (%)	43 (64.2)	24 (35.8)	
Yes, n (%)	20 (60.6)	13 (39.4)	
HT			0.248
No, n (%)	20 (55.6)	16 (44.4)	
Yes, n (%)	43 (67.2)	21 (32.8)	
DM			0.905
No, n (%)	47 (62.7)	28 (37.3)	
Yes, n (%)	16 (64.0)	9 (36.0)	
Family history			0.720
No, n (%)	48.0 (64.0)	27.0 (36.0)	
Yes, n (%)	15.0 (60.0)	10.0 (40.0)	
Diastolic BP, mmHg	83.0 ± 8.0	78.2 ± 9.9	0.013
Systolic BP, mmHg	133.1 ± 15.9	125.1 ± 15.0	0.012

Table 2. Echocardiography parameters of the enrolled patients.

	Group 1	Group 2	P-value
LVD diameter, cm	4.8 ± 0.5	4.7 ± 0.4	0.253
LVS diameter, cm	3.5 ± 0.5	3.2 ± 0.5	0.001
LA diameter, cm	3.6 ± 0.5	3.3 ± 0.4	0.005
EF, %	59.3 ± 5.7	64.9 ± 1.9	<0.001
Aortic diastolic field, cm^2	8.7 ± 2.5	7.4 ± 2.4	0.011
Aortic systolic field, cm^2	9.9 ± 2.7	9.0 ± 2.4	0.079
Aortic diastolic diameter, cm	3.3 ± 0.5	3.0 ± 0.5	0.007
Aortic systolic diameter, cm	3.5 ± 0.4	3.4 ± 0.4	0.079

fields, age, Gensini score, number of vessels, systolic BP, aortic diastolic and systolic diameters, left ventricle diastolic (LVD) diameter, and LA diameter, there was a negative correlation between the aortic stiffness index and distensibility and EF. Aortic distensibility had a positive correlation with EF, but a negative correlation was found between the aortic distensibility and other measurements such as the aortic stiffness index, aortic diastolic and systolic fields, age, Gensini score, number of vessels, systolic BP, aortic diastolic and systolic diameters, and LVD, LVS, and LA diameters (Table 3).

Table 3. Aortic stiffness index and aortic distensibility correlations.

	Aortic stiffness index		Aortic distensibility	
	rho	P	rho	P
Distensibility	–0.982	<0.001		
Aortic diastolic field	0.514	<0.001	–0.489	<0.001
Aortic systolic field	0.265	0.008	–0.245	0.014
Age	0.497	<0.001	–0.514	<0.001
Gensini score	0.450	<0.001	–0.465	<0.001
Number of vessels	0.418	<0.001	–0.437	<0.001
Diastolic BP	0.039	0.704	–0.192	0.056
Systolic BP	0.237	0.017	–0.382	<0.001
Aortic diastolic diameter	0.514	<0.001	–0.489	<0.001
Aortic systolic diameter	0.265	0.008	–0.245	0.014
LVD	0.201	0.045	–0.208	0.038
LVS	0.189	0.060	–0.208	0.038
LA	0.373	<0.001	–0.410	<0.001
EF	–0.399	<0.001	0.416	<0.001

The aortic distensibility was lower in patients with dyslipidemia. The mean aortic stiffness index was higher in patients with dyslipidemia than in those without dyslipidemia. The aortic distensibility was lower in patients with hypertension (HT). The mean aortic stiffness index was higher in patients with HT ($P < 0.001$ and $P = 0.010$; Table 4).

Regression analysis, in which factors such as age, sex, dyslipidemia, smoking, HT, diabetes mellitus (DM), family history, Gensini score, number of vessels, diastolic BP, systolic BP, LVD diameter, LVS diameter, LA diameter, EF, and aortic diastolic/systolic diameters were considered determinants of aortic stiffness and distensibility, demonstrated that the aortic stiffness index was associated with age, Gensini score, LVD diameter, LVS diameter, EF, and aortic diastolic and systolic diameters (Table 5).

Regression analysis of the model demonstrated that aortic distensibility was associated with age, diastolic and systolic BP, and diastolic and systolic diameters (Table 6).

Discussion

Currently, flexibility of the vascular bed is accepted as an important factor in atherosclerotic progression. It has been accepted that a vascular bed with decreased flexibility facilitates atherosclerotic development (19). It has been reported that a decrease in aortic flexibility accompanies advanced age (20), hypertension, DM, and dyslipidemia. Furthermore, end-stage renal insufficiency has some effects on aortic flexibility (19).

There are several hypotheses accepted about arterial stiffness. One of them suggests that aortic stiffness occurs due to long-term atherosclerosis. Experimental studies in rabbits with low-density lipoprotein receptor deficiency demonstrated that hypercholesterolemia decreased aortic compliance. Decreasing aortic compliance, cholesterol accumulation, intercellular proteoglycan dysfunction, and structural change of elastin have been reported (21). In both conditions, aortic compliance decreases.

Table 4. Mean aortic stiffness index and aortic distensibility distribution according to sex, dyslipidemia, smoking, HT, DM, and family history.

			Aortic stiffness index		Aortic distensibility	
		N	Mean	P	Mean	P
Sex	Female	33	7.7 ± 5.2	0.621	36.9 ± 51.0	0.910
	Male	67	8.0 ± 5.0		27.3 ± 17.2	
Smoking	No	33	8.0 ± 5.2	0.875	31.6 ± 38.2	0.590
	Yes	67	7.8 ± 4.8		28.1 ± 16.3	
Dyslipidemia	No	43	7.4 ± 5.4	0.139	31.9 ± 22.7	0.121
	Yes	57	8.2 ± 4.8		29.3 ± 38.5	
HT	No	36	6.4 ± 4.3	0.010	34.7 ± 18.1	0.001
	Yes	64	8.7 ± 5.3		28.1 ± 38.3	
DM	No	75	7.6 ± 5.1	0.102	32.7 ± 36.0	0.060
	Yes	25	8.8 ± 5.0		23.7 ± 17.7	
Family history	No	75	8.3 ± 5.4	0.240	29.4 ± 34.7	0.258
	Yes	25	6.6 ± 3.6		33.5 ± 25.4	

Table 5. Multifactorial regression analysis of aortic stiffness determinants.

	B	Beta	P
Coefficient	1.965		0.832
Age	0.149	0.342	<0.001
Sex	–1.344	–0.125	0.105
Dyslipidemia	–0.393	–0.039	0.586
Smoking	1.537	0.143	0.052
HT	0.159	0.015	0.860
DM	0.505	0.043	0.532
Family history	–0.546	-0.047	0.497
Gensini score	0.045	0.244	0.011
Number of vessels	–0.587	–0.152	0.180
Diastolic BP	–0.107	–0.190	0.075
Systolic BP	0.040	0.126	0.301
LVD	2.539	0.227	0.015
LVS	–2.201	–0.228	0.023
LA	1.320	0.132	0.100
EF	–0.125	–0.133	0.199
Diastolic diameter	13.612	1.302	<0.001
Systolic diameter	–12.661	–1.132	<0.001

$R^2 = 0.678$

Table 6. Multifactorial regression analysis of aortic distensibility determinants.

	B	Beta	p
Coefficient	11.459		0.636
Age	0.209	0.075	0.030
Sex	–3.653	–0.053	0.090
Dyslipidemia	0.672	0.010	0.720
Smoking	1.216	0.018	0.551
HT	–1.351	–0.020	0.563
DM	3.732	0.050	0.078
Family history	–1.136	–0.015	0.587
Gensini score	0.077	0.065	0.091
Number of vessels	0.639	0.026	0.573
Diastolic BP	0.731	0.202	<0.001
Systolic BP	–0.660	–0.324	<0.001
LVD	5.260	0.073	0.051
LVS	–0.663	–0.011	0.790
LA	–1.947	–0.030	0.348
EF	0.131	0.022	0.605
Diastolic diameter	–179.085	–2.668	<0.001
Systolic diameter	168.104	2.342	<0.001

$R^2 = 0.947$

Smoking, as a cardiovascular risk factor, has a negative effect on aortic stiffness and atherosclerosis. It causes endothelial injury, decreases prostacyclins, increases vasopressin, consumes nitric oxide, and increases thrombocyte aggregation. Moreover, it contributes to atherosclerotic development and complications by stimulating the sympathetic nervous system and affecting the lipid profile. The Pathobiological Determinants of Atherosclerosis in Youth study reported an association between smoking and premature atherosclerosis (19).

With close association, aortic stiffness has an effect on cardiovascular prognosis. This association may be explained by 3 main mechanisms (22). First, increased aortic stiffness may contribute to atherosclerotic progression, thus extending to other arteries such as the coronary and carotid (23); second, besides aortic stiffness, systolic BP and pressure on vital organs increase, contributing to the risk of atherosclerotic complications (24); and third, endothelial dysfunction is involved in aortic stiffness and atherosclerotic progression. Thus, aortic stiffness plays an important role in cardiovascular events (25).

Previous studies demonstrated that HT and DM increase aortic stiffness as determined by increased aortic strain, b index, and distensibility (26-28). In these studies, parameters were calculated by the diameters from the ascending aorta. Although

it is not fully understood which mechanisms are involved in increasing aortic stiffness by HT and DM, structural changes in the walls of the vessels, atherosclerosis in HT, and stress on the wall of the vessels from glycosylated substances in DM have been suspected (28,29). Even if the mechanisms are not obvious, it has been demonstrated that in both conditions, aortic stiffness was associated with mortality (28). In our study, in addition to the previous findings, it was determined that DM in hypertensive patients increased aortic stiffness. Thus, the increase of mortality in patients with HT and DM may be associated with aortic stiffness (30).

It is known that aortic stiffness has a direct relation with cardiovascular mortality (27). Aortic functions should be detected to determine the cardiac risk and treatment efficacy. For that purpose, it has been recommended to check the ascending aorta flexibility. The ascending aorta is supplied by the coronary arteries and it is known that flexibility in this field is affected by CAD (31). Thus, CAD may also contribute to an increase of aortic stiffness. The extension of CAD may reflect the level of aortic stiffness and, conversely, an increase in aortic stiffness is associated with severe CAD. In our study, this correlation was determined by objective findings such as the Gensini risk score, aortic stiffness index, and distensibility. This close relation between aortic stiffness and atherosclerosis will be accompanied by an increase of mortality and morbidity related with CAD. In our study, the increased extension of coronary atherosclerosis caused higher aortic stiffness, suggesting the close relation between them. Atherosclerosis and CAD extension may be determined by the noninvasive measurement of aortic stiffness. Thus, it may contribute to the improvement of cardiovascular disease prognosis by providing early diagnosis and treatment.

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