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Association of Cardiovascular Calcifications with Coronary Artery Disease

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Summary

The aim of this study was to determine whether there is a significant association between calcification of the aortic valve or thoracic aortic calcified plaques and coronary artery disease (CAD) in patients undergoing coronary angiography. If an association could be established between cardiovascular calcifications and CAD, their presence might be used as a marker of coronary atherosclerosis.

The study group consisted of 1100 patients who underwent coronary angiography. The presence of aortic valve calcification was identified by echocardiography. Chest X-rays were used to detect calcification in the thoracic aorta.

Of the 1100 patients included in the study, 812 (73.8 percent) had CAD, and 288 (26.2 percent) had normal coronary arteries. Aortic valve calcification was present in 420 (38%) and aortic calcified plaques in 180 (16%) of the entire study population. The patients with aortic valve calcification had a significantly higher prevalence of CAD (88% vs 65%, p<0.0001) and higher rates of multivessel disease (65% vs 55%, p=0.003). Also, the prevalence of CAD (86% vs 71%, p<0.0001) and multivessel disease (66% vs 57%, p=0.035) were significantly higher in patients with aortic calcified plaques compared with the patients without aortic calcified plaques. Logistic regression analysis showed that aortic valve calcification (p=0.003) and aortic calcified plaques (p=0.004) were strongly and significantly associated with CAD after adjusting for coronary risk factors. In addition, patients with aortic valve calcification had a high incidence of aortic calcified plaques (23% vs. 12%, p<0.0001).

In conclusion, we found a significant association of CAD with the presence of aortic valve calcification and aortic calcified plaques. Our study further demonstrates that aortic valve calcification is significantly associated with calcified plaques in the thoracic aorta. Therefore, the presence of these calcifications should be regarded as a sign for the presence of CAD. ***(Türk Kardiyol Dern Arş 2004; 32: 364-370)***

Key words: *Atherosclerosis, calcification, coronary artery disease*

Özet

Kardiyovasküler Kalsifikasyonlar ile Koroner Arter Hastalığı Arasındaki İlişki

Çalışmanın amacı koroner anjiyografi yapılan hastalarda, torasik aortadaki aterom plağı kalsifikasyonu veya aort kapak kalsifikasyonu ile koroner arter hastalığı arasındaki ilişkiyi incelemektir. Kardiyovasküler kalsifikasyonlar ile koroner arter hastalığı arasında ilişki olması durumunda, bu kalsifikasyonlar koroner aterosklerozun göstergesi olarak kullanılabilir.

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Çalışmaya koroner anjiyografi yapılan 1100 hasta alındı. Aort kapak kalsifikasyon varlığı ekokardiyografi ile değerlendirildi. Torasik aortadaki kalsifikasyonları saptamak için PA akciğer grafisi kullanıldı.

Çalışmaya alınan 1100 hastanın 812'sinde (%73.8) koroner arter hastalığı saptanırken, 288'inde (%26.2) koronerler normal bulundu. Hastaların 420'sinde (38%) aort kapak kalsifikasyonu ve 180'inde (16%) torasik aorta plak kalsifikasyonu saptandı. Aort kapak kalsifikasyonu saptanan hastalarda, koroner arter hastalığı sıklığı (%88 karşı %65, p<0.0001) ve çok damar hastalığı oranı (%65% karşı %55, p=0.003) daha yüksek bulundu. Koroner arter hastalığı sıklığı ve çok damar hastalığı oranı, torasik aorta plak kalsifikasyonu saptanan hastalarda da yüksek bulundu (sırasıyla, %86 karşı %71, p<0.0001 ve %66 karşı %57, p=0.035). Logistik regresyon analizi ile koroner arter hastalığı risk faktörlerine göre düzeltme yapıldıktan sonra bile, aort kapak kalsifikasyonu (p=0.003) ve torasik aorta plak kalsifikasyonu (p=0.004), koroner arter hastalığı ile ilişkili bulundu. Aort kapak kalsifikasyonu olan hastalarda, torasik aorta plak kalsifikasyonu daha sık izlendi (%23% karşı. %12, p<0.0001).

Sonuç olarak, çalşımamızda aort kapak kalsifikasyonu ve torasik aorta plak kalsifikasyonları ile koroner arter hastalığı arasında anlamlı ilişki saptadık. Ayrıca, aort kapak kalsifikasyonu ile torasik aorta plak kalsifikasyonu anlamlı olarak ilişkili idi. Kardiyovasküler kalsifikasyonların varlığı koroner arter hastalığı için bir gösterge olarak düşünülebilir. ***(Türk Kardiyol Dern Arş 2004; 32: 364-370)***

Anahtar kelimeler: *Ateroskleroz, kalsifikasyon, koroner arter hastalığı*

Aortic valve calcification and coronary atherosclerosis share many risk factors [1-6] in common and a possible association of aortic valve calcification with coronary artery disease (CAD) has been suggested [5-12]. The presence of calcified plaques in the abdominal or thoracic aorta was also found to be strongly related to CAD or cardiovascular death [13-16]. However, cardiovascular events were used to indicate the presence of CAD in some of these studies. This can lead to misclassification bias and inaccurate conclusions because many more individuals will actually have CAD than are indicated by the percentage of the cohort defined as abnormal only after clinical end points are manifest.

If an association could be established between aortic valve calcification or calcified plaques in the thoracic aorta and CAD, the presence of these calcifications may be a marker for the CAD in patients undergoing coronary angiography. Therefore, the aim of our study was to determine whether there is a significant association of calcification of aortic valve or calcified plaques in the thoracic aorta and CAD.

MATERIAL and METHODS

The study group consisted of patients who underwent routine coronary angiography for various clinical indications. The patients with rheumatic valvular disease, prosthetic valves, or with technically suboptimal echocardiograms were excluded. Patients with aortic and/or mitral stenosis were also excluded. The study was approved by the Ethical Committee of our institution, and informed consent was obtained from each patient before participation in the study.

Echocardiography: Echocardiographic examinations were performed in the left lateral decubitis positions with a commercially available echo and Doppler system. Aortic valve calcification was defined as thickening of the aortic valve leaflets with dense echoes originating from the aortic valve without restricting the leaflet motions. Doppler echocardiographic examinations of the cardiac valves were performed under color flow guidance from the parasternal and apical views. Aortic stenosis was defined as having a maximum pressure gradient exceeding 16 mm Hg. Because it is not possible to distinguish whether an increased reflection originates from a calcific or a sclerotic (dense fibrosis without calcification) cardiac structure, the term "calcification" is used to indicate true calcification as well as dense fibrosis in our echocardiographic descriptions. All echocardiograms were interpreted without the knowledge of other clinical or laboratory information.

Coronary angiography: Selective coronary angiography was performed in multiple orthogonal projections using the Judkins' or Sones' techniques. Coronary arteriograms were reviewed by 2 independent experienced observers who were blinded to the clinical data. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, and epicardial local or diffuse caliber reduction and stenosis. CAD was defined by visual assessment as any lesion with a 20 percent diameter stenosis in any major coronary artery, including large diagonal and marginal vessels. Coronary arteries were classified as normal based on visual assessment of absence of any luminal irregularities. Coronary angiograms with luminal wall irregularities but no stenosis greater or equal to 20 percent narrowing were not included in the study because we think that it is very hard to dichotomize these patients as having CAD without intravascular ultrasound examination. Fourty-six patients with luminal wall irregularity were excluded, and the remaining 1100 patients were included in the study.

Chest x-rays: Routine chest x-rays of the patients was used to detect calcification in the thoracic aorta. Aortic calcified plaques were considered present when typical calcific densities were seen in the aortic arch or in the descending part of the thoracic aorta. The presence or absence of aortic calcified plaques was determined by 2 observers. Any disagreement were resolved by consensus.

Coronary risk factors: The risk factors recorded in this study were age, gender, diabetes mellitus, hypertension, hypercholesterolemia, and history of smoking. Diabetes was considered present if the subject was receiving insulin or an oral hypoglycemic agent. Hypertension was considered present when blood pressure recordings was greater than 140/90 or the subject was receiving antihypertensive therapy. Hypercholesterolemia was judged to be present when the subject was receiving cholesterol lowering therapy or when the total serum cholesterol concentration was 200 mg/dL. Cigarette smoking was defined as smoking of a half pack of cigarettes or more per day.

Statistical analysis: Continuous variables were expressed as mean ± SD. Comparison of the continuous variables was done with the unpaired Student t test. The chi-square test with Yates' continuity correction was used to assess the significance of difference between dichotomous variables. Independent risk factors for coronary artery disease, aortic valve calcification, and aortic calcified plaques were determined by stepwise logistic regression analysis. The following variables were induded into the analysis: age, gender, hypertension, diabetes mellitus, hypercholesterolemia, and history of smoking. Then, in order to evaluate whether aortic valve calcification, and aortic calcified plaques are an independent factor for the presence of CAD, these variables were separately forced into the analysis. For all tests, P values lower than 0.05 were considered statistically significant. All statistical analysis was performed with SPSS statistical software package (version 7.0).

RESULTS

Of the 1100 patients included in the study, 812 (73.8 percent) had CAD, and 288 (26.2 percent) had normal coronary arteries. Table 1 shows the baseline characteristics and the comparison of the echocardiographic variables measured in patients with CAD and normal coronary arteries. As expected, patients with CAD were older, more often males, had a higher frequency of coronary risk factors. Left atrium, aorta, and left ventricular dimensions were greater in subjects with CAD than in those with normal coronary arteries. Although no significant differences were observed in the incidence of aortic regurgitation in patients with or without CAD, the incidence of mitral regurgitation was higher in patients with CAD. The incidence of aortic valve calcification and aortic calcified plaques were significantly higher in patients with CAD compared to patients with normal coronary arteries.

Reasons for referral to coronary angiography were not different between patients with and without calcifications (table 2). Myocardial infarction was the leading cause in all groups, followed by stable/unstable angina pectoris and atypical angina pectoris.

The patients with aortic valve calcification had a significantly higher prevalence of CAD (88% vs 65%, $p<0.0001$) and higher rates of multivessel disease (65% vs 55%, $p=0.003$). Also,

Table 1. Baseline characteristics, echocardiographic findings, and frequency of calcifications

	All patients (n=1100)	Coronary artery disease (n=812)	Control (n=288)	*p value
Clinical characteristics				
Age (year)	63 ± 11	64 ± 10	58 ± 10	<0.001
Women	329 (29.9%)	165 (20.3%)	164 (56.9%)	
Men	771 (70.1%)	647 (79.7%)	124 (43.1%)	<0.00001
Hypercholesterolemia	605 (55%)	476 (58.6%)	129 (44.8%)	0.00003
Diabetes Mellitus	202 (18.4%)	172 (21.2%)	30 (10.4%)	0.00008
Hypertension	482 (43.8%)	386 (47.5%)	96 (33.3%)	<0.00001
Smoking	583 (53%)	484 (59.6%)	99 (34.4%)	<0.00001
Echocardiographic characteristics				
Aortic regurgitation	156 (14.2%)	122 (15.0%)	34 (11.8%)	0.1486
Mitral regurgitation	286 (26%)	239 (29.4%)	47 (16.3%)	0.00001
Aorta diameter (mm)	30.4 ± 4.2	30.9 ± 3.6	28.9 ± 5.2	<0.001
Left atrial diameter (mm)	35.9 ± 4.6	36.4 ± 4.4	34.6 ± 4.9	<0.001
Ejection fraction (%)	62.7 ± 8.3	61.2 ± 8.5	66.7 ± 6.0	<0.001
LVDD (mm)	51.4 ± 6.0	52.3 ± 6.2	48.9 ± 4.7	<0.001
LVDS (mm)	36.2 ± 5.8	37.3 ± 5.9	33.4 ± 4.3	<0.001
Calcifications				
Aortic valve calcification	420 (38.2%)	368 (45.3%)	52 (18.1%)	<0.00001
Aortic calcified plaques	180 (16.4%)	155 (19.1%)	25 (8.7%)	0.00004

*Data are expressed as mean value ± SD or number (%) of subjects. LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; *between coronary artery disease and control groups*

the prevalence of CAD (86% vs 71% p<0.0001) and multivessel disease (66% vs 57% p=0.035) were significantly higher in patients with aortic calcified plaques compared the patients without it. In addition, the patients with aortic valve calcification had a significantly higher prevalence of aortic calcified plaques (23% vs 12%, p<0.0001).

Logistic regression analysis showed that aortic valve calcification (p=0.003) and aortic calcified plaques (p=0.004) were strongly and significantly associated with CAD after adjusting for coronary risk factors. Multivariate analysis showed that significant risk factors for aortic valve calcification and aortic calcified plaques were age (p<0.0001, p<0.0001, respectively), hypertension (p=0.003, p=0.002, respectively), and hypercholesterolemia (p=0.023, p=0.014, respectively). Diabetes mellitus was also a risk factor for aortic valve calcification (p=0.0009) but not for aortic calcified plaques.

DISCUSSION

We found that the subjects with aortic valve calcification had a higher chance of having CAD than those without aortic valve calcification, after controlling the confounding effects

Table 2. Reasons for coronary angiography in patients with and without calcifications

Reason for coronary angiography	AVC (+) (n=420)	AVC (-) (n=680)	ACP (+) (n=180)	ACP (-) (n=920)
Atypical angina pectoris	88 (21%)	150 (22%)	43 (24%)	195 (21%)
Stable/unstable angina pectoris	139 (33%)	199 (29%)	48 (27%)	290 (32%)
Myocardial infarction	193 (46%)	331 (49%)	89 (49%)	435 (47%)

AVC, Aortic valve calcification; ACP, aortic calcified plaques. There were no significant differences between groups.

Table 3. Prevalence and characteristics of coronary artery disease in patients with and without aortic valve calcification and aortic calcified plaques.

	AVC (+) (n=420)	AVC (-) (n=680)	p	ACP (+) (n=180)	ACP (-) (n=920)	p
CAD	369 (%88)	444 (%65)	<0.0001	155 (%86)	657 (%71)	<0.0001
1-vessel CAD	131 (36%)	202 (46%)	0.009	52 (34%)	281 (43%)	0.027
2-vessel CAD	141 (38%)	152 (34%)		70 (45%)	223 (34%)	
3-vessel CAD	97 (26%)	90 (20%)		33 (21%)	153 (23%)	
2 or 3-vessel CAD	238 (65%)	242 (55%)	0.003	103 (66%)	376 (57%)	0.035

CAD, coronary artery disease; AVC, Aortic valve calcification; ACP, aortic calcified plaques.

of cardiovascular risk factors. Two current clinical studies have examined the relation of aortic valve calcification with cardiovascular events. Aronow et al [8], have noted that older subjects with aortic valve sclerosis had a higher incidence of new coronary events than older subjects without aortic valve calcification. Otto et al [5] have shown that the presence of aortic valve sclerosis was associated with an increased risk of both death from cardiovascular causes and new myocardial infarction. Several recent studies have shown a significant association between AVC as detected by transthoracic echocardiography and significant CAD in patients undergoing coronary angiography [10-12]. In addition, AVC as detected with electron beam tomography was found to be associated with the angiographic extent and severity of CAD[9]. Our results support these findings in a larger population.

Further support for the association between aortic valve calcification and CAD comes from pathological studies. It has been shown that the early lesions of degenerative aortic valve disease has some similarities to that of atherosclerosis, including lipid deposition, and inflammatory cell infiltration [17-19]. Thubrikar et al showed that experimentally induced atherosclerosis is associated with the fatty plaques deposits on the aortic and mitral valve [20].

In our study, the subjects with aortic calcified plaques had a higher probability of having CAD than those without aortic calcified plaques after adjustment for cardiovascular risk factors. In agreement with the present results, the Framingham study has showed that the presence of aortic calcified plaques in the thoracic aorta was significantly associated with an increased risk of both clinically defined CAD and death from cardiovascular causes [14]. In aggrement with our study, Li et al demonstrated an association between CAD and aortic arch calcification on plain chest radiography [16]. In addition, thoracic aortic calcification as detected by com-

puted tomography was found to be related to CAD [15]. It has also been shown that the presence of aortic atheromas detected by transesophageal echocardiography is strongly associated with CAD [21-22].

Several investigators have studied risk factors for their association with aortic valve calcification. Age, gender, hypertension, hypercholesterolemia, low HDLc, elevated levels of LDLc, increased Lp(a), diabetes, low body mass index, height, cigarette smoking have all been shown to be associated with aortic valve calcification in one or more studies in one or more patient groups [1-4,6]. Age and hypertension have most consistently been shown to be associated with aortic valve calcification. Associations of other risk factors with aortic valve calcification have varied among studies. Aronow et al.[1] identified an association between aortic valve calcification and hypertension, diabetes, hypercholesterolemia and low HDLc. Gotoh et al [3] found that increased serum levels of Lp(a), as well as aging, are significantly related to aortic valve sclerosis. In the Helsinki Aging Study [2], hypertension, age and a low body mass index were strongly associated with aortic valve calcification. In the Cardiovascular Health Study [4], age, gender, height, hypertension, smoking, Lp (a) and LDLc were significant risk factors for degenerative aortic valve disease. Our study showed that age, hypertension, hypercholesterolemia, and diabetes mellitus are independent risk factors for aortic valve calcification.

We found that age, hypertension, and hypercholesterolemia are important risk factors for aortic calcified plaques. In Framingham study, age, gender, hypertension, and serum cholesterol level were found to be associated with aortic calcified plaques [14]. In our study, gender was not emerged as a significant risk factor for aortic calcified plaques.

Limitations of study: The principal limitations of our study are that it is a cross-sectional analysis and the number of subjects in the control group is relatively small compared to the number of subjects in the CAD group. We defined CAD as any lesion with a ≥20 percent diameter stenosis. Although there is no definite absolute criteria, generally a 50% cut-off are used in the literature. We think that the patients with greater than 20 percent but less than 50 percent stenosis constitute an important group that might benefit from early diagnosis of coronary atherosclerosis. Although multivariate analysis was performed to adjust for atherosclerotic risk factors, unevaluated factors may have contributed to our findings. The specificity of echocardiography for detection of aortic valve calcification is not perfect. Also, misclassification of chest x-ray of thoracic aorta may have occurred. However, misclassification is likely to be random. Finally, control subjects in this study are members of a group of patients referred for coronary angiography and may not represent true normal population although their coronary angiograms are totally normal.

Summary: Previous studies and our data suggest that aortic valve calcification, and aortic calcified plaques may not be simply a benign age-associated degenerative process but instead may be a marker for the presence of CAD and hence an increased risk of cardiovascular events. Our study further demonstrates that aortic valve calcification and aortic calcified plaques are significantly associated with each other. Therefore, it is reasonable to suggest a common etiologic basis for these calcifications and coronary atherosclerosis, and their presence should be regarded as a sign for the presence of CAD.

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