Journal Of
Cardio-Thoracic Medicine

www.jctm.mums.ac.ir

Correlation Between Aortic Valve Sclerosis and Coronary Artery Disease: A Cross - Sectional Study

Afsoon Fazlinezhad[1], Leila Hosseini[2], HadisYousefzadeh[3], Saied Akhlaghi[4]

[1] Cardiologist,Cardiovascular Research Center, Cardiology Department of Ghaem Hospital, Mashhad University of Medical Sciences ,Mashhad, Iran
[2] Cardiologist, Health center,Mashhad University of Medical Sciences ,Mashhad, Iran
[3] Student of Immunology (PhD), Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran
[4] Statistician, Mashhad University Medical Sciences, Mashhad, Iran

ARTICLE INFO

Article type:
Original article

Article history:
Received:21 Nov 2012
Revised:2 Jan 2013
Accepted : 15 Jan 2013

Keywords:
angiography
Aortic valve Sclerosis
echocardiography

ABSTRACT

Introduction: Aortic valve sclerosisis considered as a manifestation of coronary atherosclerosis. Recent studies demonstrated an association between aortic valve sclerosis and obstructive coronary artery disease. The purpose of this study was to evaluatethe correlation betweenaortic valve sclerosis andobstructive coronary artery disease and the extent of coronary artery disease in patients hospitalized for chest pain.
Materials and Methods: A total of 230 consecutive patients were referred to the coronary angiography of GhaemMedical Center and were subjected to transthorasic echocardiography for screening of aortic valve sclerosis and coronary risk assessment. The diagnostic value of obstructive coronary artery disease for aortic valve sclerosis was calculated.
Results: The patients with obstructive coronary artery disease had a higher prevalence of aortic valve sclerosis compared to those with no coronary artery disease (P< 0.05). Aortic valve sclerosis was an independent predictor for obstructive coronary artery disease by multivariate analysis (P< 0.05). Aortic valve sclerosis had sensitivity of 47% and specificity of 79% and positive predictor value of 92%.
Conclusions: Aortic valve sclerosis was an independent predictor for obstructive coronary artery disease in patients with chest pain and was strongly interrelated with the extent of coronary artery disease in these patients.

Introduction

Aortic valve sclerosis (AVS) is defined as a progressive calcification, increased thickening of aortic valve leaflets without valve obstruction and antegrade velocity across the valve less than 2.5 m/s (1). AVS presence is associated with an approximately 50% increase in cardiovascular mortality and myocardial infarction (2).

AVS's predictive value among cardiovascular findings in these patients is limited (3). Echocardiography scanning of individuals without coronary artery disease (CAD) symptoms is cost-prohibitive so finding existing subgroups of cases with AVS at a high risk for heart disease was necessary. Over the last decade, different researchers evaluated the relationship between AVS and CAD (4) but studies about AVS's importance as a single factor in classification of risk is limited.The association between CAD and AVS could be clearly seen in ischemic heart suspected patients who had coronary angiography(5). AVS was also documented as a strong predictor of obstructive CAD (obCAD) and it might be considered as a CAD risk stratification (6). Thus, the determination of the degree of AVS is the most imperativerisk for CAD and should be investigated.

The purpose of this study was to evaluate whether the presence and severity of AVS in echocardiographic evaluation could be a predictor for obCAD severity. The extent of CAD in patients hospitalized for chest pain is of concern given the number and vital importance of the in-

* *Corresponding author:* Fazlinezhad A, MD, Cardiovascular ResearchCenter, Cardiology Department of GhaemHospital, Mashhad University of Medical sciences (MUMS), Ahmadabad St., Mashhad,Iran, Tel: +989153134470, Fax: +985118430492, *E-mail:* fazlinejada@mums.ac.ir

volved vessels. We are looking to address the special importance in risk acceptance for patients who have had a moderate risk for CAD.

Materials and Methods

Study population

This cross-sectional study included 230 patients with chest pain who were known or clinically suspected cases of CAD and scheduled for coronary angiography between March 2008 and August 2009 in Ghaem University Hospital, Mashhad, Iran. Clinical history and laboratory data were collected from all patients. All patients underwent complete transthorasic echocardiography (TTE) prior to considering coronary angiography either on the same day or within 2 days of the procedure. Patients with aortic stenosis, aortic regurgitation more than mild, rheumatic valvular disease, congenital heart disease history and prosthetic valve replacement were excluded from the study. An informed consent form was obtained from all patients. All procedures were approved by ethics committee of Mashhad University of Medical Sciences (MUMS).

Clinical data

All patients' demographic characteristics and atherogenic risk factors were determined before they underwent coronary angiography. Diabetes mellitus, systemic hypertension, hyperlipidemia and renal failure were defined as hyperglycemia more than 114 mg/dl fasting blood sugar or diabetes medications, blood pressure>140/90 mmHg or antihypertensive medications, LDL>110mg/dl and total cholesterol level > 200 mg/dl, and creatinine more than 1.3 mg/dl, respectively. Smoking was defined as active smoking within the past 12 months.

Electrocardiographic (ECG) changes including ischemic ST-T changes, Q-wave, bundle branch block and arrhythmia were evaluated and diastolic dysfunction rely on mitral valve filling pattern and mitral annular tissue Doppler imaging were classified into defined categories such as; impaired left ventricular relaxation, pseudo normalized and restrictive pattern.

Echocardiographic Evaluation

Complete TTE studies were performed according to the last ASE-AHA guidelines for all patients using commercially available system (VIVID7 dimension, GE, Horten Norvey, 2007with probe 2.5-3.5 MHZ) in lying down and left lateral positions. Two dimensional assessments of the aortic valve were made from the parasternal long axis, short axis and apical views with appropriate gain settings. Peak transaortic flow velocity was measured from the apical view by continuous wave Doppler. AVS was defined as a focal area of increased echogenicity and thickening of the aortic valve leaflets without restriction of leaflet motion and a transaortic flow velocity (<2.5 m.s) on TTE (2, 7). The thickness of sclerotic aortic cusps were determined from the end diastolic frozen echocardiographic images obtained in either short or long axis. Mild, moderate and severe AVS were classified as cusp thickness 2-3.9 mm, 4-6 mm and >6 mm, respectively (8, 9). Mitral annular calcification (MAC) was also evaluated and measured from the 2 and 4 chamber views. MAC was defined as thickness increment of mitral annulus >5 mm (8).

Coronary angiography

Coronary angiography in multiple views was performed according Judkins or Sones Standard technique (10). At least four views for evaluation of left main (LM) coronary artery, left anterior descending (LAD), left circumflex (LCX) and right coronary artery (RCA) were performed. Angiographic results were interpreted by angiographer who was blinded to echocardiographic findings. Significant CAD was defined as more than 50% reduction of internal diameter of at least one coronary artery. The definition of 1-, 2- or 3- vessel disease was based on the criteria of Coronary Artery Surgery study (11).

Statistical analysis

Student'st-test or Mann-Whitney test was used to compare the continuous data, according to the presence and absence of AVS or ObCAD. Furthermore, group comparisons involving categorical data were made using chi-square analyses. Correlation between severity of ObCAD and other variables was investigated by Spearman's correlation coefficient and ANOVA or Kruskal Wallis test. Multiple logistic regression analysis was applied to evaluate the association of significant ObCAD with AVS and other coronary risk factors. Pvalue less than 0.05 was considered significant. Numerical data are expressed as mean ± SD or as proportions of the sample size.

Results

Patient's clinical characteristics

The baseline characteristics of patients underwent coronary angiography were presented in Table 1. The CAD group included 184 patients (123 male and 61 female; mean age 61.49 ±10.85 years) and the non CAD group included 34 patients (15 male and 19 female; mean age 57.41±9.8 years). There was a higher proportion of elderly patients (age more than 60 years old) in CAD group compare to non CAD group (P< 0.05). Diabetes mellitus, hypertension, hyperlipidemia, renal failure, smoking history and ECG ischemic changes were also more common in CAD patients. However, these increments were not significant. Cases with CAD had a higher prevalence

Table 1. Baseline Characteristics of Patients With and Without Coronary Artery Disease (CAD)

Variables	No CAD (n=46)	CAD (n=184)	Odd ratio	95% CI	P-valve
Sex (Male)	15 (24.1%)	123 (66.8%)	2.56	(0.18-0.82)	0.087
Age ≥ 60 y	15 (44.1%)	110 (61.1%)	1.99	(0.94-4.17)	0.019
Age (year)	57.41 ± 9.8	10.85 ± 61.49	2.03	(0.89-4.61)	0.089
Diabetes mellitus	10 (30.3%)	46 (25.4%)	0.78	(0.34-1.76)	0.520
HTN	17 (51.5%)	98 (54.1%)	1.11	(0.52-2.33)	0.850
HLP	14 (42.4%)	75 (41.4%)	0.96	(0.45-2.03)	1
RF	0 (0.0%)	3 (1.7%)	_	_	1
Smoking	6 (18.2%)	31 (17.1%)	0.93	(0.35-2.44)	0.808
ECG Ischemic	21 (65.6%)	101 (59.4%)	0.76	(0.348-1.69)	0.56
Diastolic dysfunction	5 (15.2%)	50 (29.1%)	2.29	(0.83-6.28)	0.079
MAC	2 (5.9%)	9 (4.9%)	0.818	(0.169-3.96)	0.682
AVS	7 (20.6%)	88 (47.6%)	3.49	(1.45-8.43)	0.004
Sclerotic RCC	6 (17.6%)	71 (38.6%)	2.93	(1.15-7.43)	0.019
Sclerotic NCC	6 (17.6%)	76 (41.3%)	3.28	(1.29-8.31)	0.011
Sclerotic LCC	2 (5.9%)	30 (16.3%)	3.11	(0.70-13.7)	0.184
EF	0.54±0.08	0.49±0.12			

Data werepresented as mean± SD or percent of patients; CI= confidence interval; HTN= Hypertension; HLP= Hyperlipidemia; RF= Renal Failure; MAC= Mitral annular calcium; AVS= Aortic valve sclerosis; RCC= Right Coronary Cusp; NCC= Non Coronary Cusp; LCC= Left Coronary Cusp; EF= Ejection Fraction

of AVS than those without CAD (P< 0.01). Also non coronary cusp (NCC) and right coronary cusp sclerosis (RCC) in CAD patients were significantly higher than non CAD patients (P<0.05).

Echocardiographic findings

Table 2 summarizes the clinical and laboratory characteristics of the cases with and without AVS. Echocardiographic findings revealed that among 103 patients who had AVS, 88 were found to have significant obCAD compared to 97 cases out of 127 patients without AVS (P<0.01). AVS prevalence in Age>60 years was significantly higher than younger patients (P<0.001).

Patients with AVS revealed higher prevalence of respected diastolic dysfunction stages (I, II and III stages, respectively) in comparison with patients without AVS (P<0.01) (Table2). The distribution of coronary artery involvement in different stages of AVS is shown in Fig 1.

There was significant difference in extent of coronary arteries between patients with AVS and without AVS (P<0.001). There was also significant increase in LCX and RCA involvement in AVS patients (P<0.05, <0.001, respectively) compare to patients without AVS.

Multiple logistic regression analysis

Multiple logistic regression analysis was conducted to determine the association between obCAD with some clinical variables including AVS, diastolic dysfunction, ECG ischemia, mitral annular calcium, and age >60 years. Data has been revealed in Table 3. The analysis presented AVS as a significant predictor of the CAD presence in patients with suspected ischemic heart disease. The prevalence of CAD in patients with AVS were3 times higher than patients without AVS (OR=3.49).

Among aortic cusps involved in patients with AVS, RCC and LCC had the maximum and minimum of sclerosis, respectively (55.07% versus12.5%).Univariate analysis revealed that RCC and NCC sclerosis and their severity had significantly correlated with obCAD (P<0.001). Likewise there was significant linear correlation between RCC, NCC, LCC sclerosis severity with severity of obCAD (P<0.001).

Figure 1. Distribution of coronary artery involvement in different stages of aortic valve sclerosis
LM (Left main), VD (Vessel Disease)

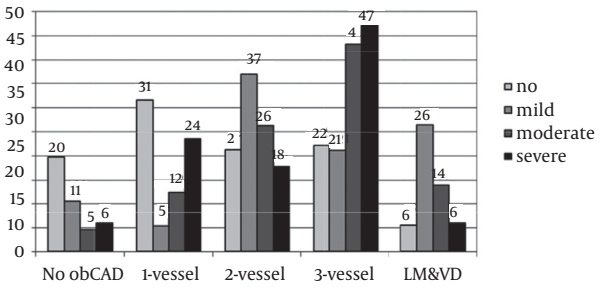

Table 2. Clinical Characteristics of Patients With And Without Aortic Valve Sclerosis (AVS)

Variable		Without AVS (n=127)	AVS (n=103)	P valve
Male		75 (59.1%)	70 (67.9%)	0.168
Age ≥ 60 y		58.59 ± 10.06	64.17 ± 10.86	< 0.001
Age (year)		67 (52.8%)	65 (67.0%)	0.040
Diabetes mellitus		34 (27.4%)	24 (23.8%)	0.540
HTN		63 (50.8%)	58 (57.4%)	0.349
HLP		57 (46.0%)	37 (36.6%)	0.176
RF		1 (0.8%)	2 (2.0%)	0.589
Smoking		22 (17.7%)	17 (16.8%)	1
MAC		4 (3.1%)	9 (8.7%)	0.087
Diastolic dysfunction	Stage 1 & NL	94 (77/0%)	62 (67.4%)	0.004
	Stage 2	26 (21.3%)	18 (19.6%)	
	Stage 3	2 (1.6%)	12 (13.0%)	
Ob CAD		97 (78.2%)	88 (96.6%)	0.004

Data were presented as mean± SD or percent of patients; HTN = Hypertension; HLP= Hyperlipidemia; RF= Renal Failure; MAC= Mitral annular Calcification; obCAD= obstructive coronary artery disease.

Table 3. Relation Between Some Variables in Different Sclerosis Severity in Obcad Patients

Variables	NL	1-VD	2-VD	3-VD	LM=VD	P value
Sex Male	10 (32.3%)	33 (62.3%)	37 (68.5%)	50 (72.5%)	15 (68.2%)	0.002
Age ≥ 60 y	11 (35.5%)	26 (50%)	33 (61.1%)	50 (75.8%)	12 (57.1%)	0.001
Diabetes mellitus	6 (20.7%)	11 (21.2%)	12 (22.2%)	23 (33.3%)	6 (28.6%)	0.118
HTN	16 (55.2%)	24 (46.2%)	26 (48.1%)	40 (58%)	15 (71.4%)	0.115
HLP	14 (48.3%)	20 (38.5%)	24 (44.4%)	29 (42%)	7 (33.3%)	0.57
RF	0	0	0	2 (2.9%)	1 (4.8%)	0.047
Smoking	4 (13.8%)	12 (23.1%)	10 (18.5%)	8 (11.6%)	5 (23.8%)	0.654
Sclerotic RCC	5 (6.2%)	12 (14.8%)	18 (22.2%)	34 (42%)	12 (14.8%)	<0.001
Sclerotic NCC	5 (5.7%)	11 (12.5%)	23 (26%)	36 (40.9%)	13 (14.8%)	<0.001
Sclerotic LCC	1 (2.9%)	3 (8.8%)	10 (29.4%)	3 (8.8%)	3 (8.8%)	<0.004

Data werepresented as number (%) of patients, HTN=hypertension;HLP=Hyperlepidemia; RF=Renal Failure; RCC=Right Coronary Cusp; NCC=Non Coronary Cusp; LCC=Left Coronary Cusp; LM=Left main; VD=Vessel Disease.

AVS existence was effective on LCX,RCA and LM obstruction and the possibility of their obstructions were approximately 3.2-3.5 times higher in patients who had AVS compare to patients who did not represent AVS respectively (P<0.001).

Additionally, analysis showed that only sclerosis of RCC had relation with LAD obstruction (P<0.05) while sclerosis severity of all aortic trileaflets related significantly with LCX obstruction (P<0.01) and RCA obstruction (P<0.05).

Diagnostic value of AVS for CAD

Significant AVS had sensitivity and specificity of 47% and 79% for obCAD diagnosis, respectively (consider to mentioned criteria). Despite a low negative predictive value (21%), it was a high positive predictive value (PPV) (92%) for the presence of significant CAD.

Discussion

Our results indicated that AVS is a strong echocardiographic predictor for obCAD in patients with chest pain who underwent angiography. The chance of obstruction of coronary vessels in AVS patients is three times higher compare topatients without AVS.

Conte *et al* studied patients with chest pain and negative cardiac enzymes which are candidate for angiogra-

phy(4). They found AVS by TTE in patients who had high risk acceptance for obCAD (4). Hsu *et al*and Soydinc *et al* independently achieved the similar results(12, 13). Soydinc *et al* also showed the significant relation between AVS with extent and severity of CAD according to Gensini score (13). Contrarily, Tolstrup and coworkers showed that the relation between AVS and obCAD was not significant(6).

Our results showed that AVS is more prevalent in patients older than 60 years. It was exhibited that the prevalence of AVS is high and associated with aortic atheromatous diseases in people older than 60 years and 50% risk increment of angina, stroke, congestive heart failure, myocardial infarction and death (6). It has been shown that AVS is detectable by echocardiography in 50% of the elderly patients (14). Prevalence of unassigned AVS in elderly cases without aortic stenosis is common and involved 21-26% cases older than 65 years (5-7, 14-17). Clinical factors were associated with AVS pathogenesis include age, sex, hypertension, hyperlipidemia, diabetes mellitus and current smoking (7,15-16). Ejection Fraction (EF) average in obCAD patients was lower than non obCAD group, as well. High PPV measurement of our data is parallel to rest of literature (92%)(4, 6, 12).

While Hsu *et al* observed no significant correlation between the degree of aortic cusp thickening and the extent of CAD (11); our results indicate prognostic predictable value for the degree of aortic valve sclerosis in obCAD as well as a significant correlation with the extent of coronary artery involvement. In addition, between moderate and severe sclerosis, the most obCAD was observed in 2-vessel and left main involvement. We found that AVS had significant correlation to LM, RCA and LCX obstruction. Our study classified sclerosis according to leaflets thickness while with using of different kinds of morphological sclerosis better results could be achieved. Although morphological evaluation of AVS showed that this could be as obCAD predictor (8), studies about the relation between sclerosis leaflet involvement and obCAD severity are limited. Other associated factors to obCAD extent and number of involved arteries included: age more than 60 years old, male gender, ischemic changes of ECG and chronic renal failure.

Otto *et al* reported that in AVS often NCC becomes involved (2) while we found that RCC were the most involved cusp. Correspondingly we found that presence and severity of RCC and NCC sclerosis related to obCAD persistence. There was significant relation between the extent of coronary artery involvement with sclerosis of aortic leaflets and number of obstructed vessels. That meant that more than 40% of patients with NCC and RCC sclerosis had 3-VD involvement. Also, we evaluated aortic leaflet sclerosis in relation to the kind of involved vessel. We concluded that only RCC sclerosis severity was related to LAD obstruction while sclerosis of all trileaflets was associated to LCX and RCA. Stewart *et al* showed that age increment and high LDL correlated with aortic sclerosis (7), while another presented only age and lower BMI related to AVS persistence (12). Our study presented that age more than 60 years old, ECG ischemic changes and diastolic dysfunction had significant relation to AVS persistence.

Conclusion

AVS is valuable independent predictor for obCAD and degree of sclerosis is a prognostic marker of CAD and also had a significant correlation with the extent of coronary artery involvement.

Acknowledgement

The authors would like to thank vice chancellery of Research of Mashhad University of Medical Sciences, Mashhad Iran. for financial support.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Otto CM. Why is aortic sclerosis associated with adverse clinical outcomes? J Am CollCardiol 2004; 43: 176-8.
2. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic valve sclerosis with cardiovascular mortality in the elderly.N Engl J Med 1999; 341:142-7.
3. Rabkin SW. The association of hypertension and aortic valve sclerosis. Blood Press 2005; 14: 264-72.
4. Conte L, Rossi A, Cicoira M, Bonapace S, Amado EA, Golia G, et al. Aortic valve sclerosis: a marker of significant obstructive coronary artery disease in patients with chest pain? J Am SocEchocardiogr 2007; 20: 703-8.
5. Sui SJ, Ren MY, Xu FY, Zhang Y. A high association of aortic valve sclerosis detected by transthoracic echocardiography with coronary arteriosclerosis.Cardiol 2007; 108: 322-30.
6. Tolstrup K, Crawford MH, Roldan CA.Morphologic characteristics of aortic valve sclerosis by transesophageal echocardiography: importance for the prediction of coronary artery disease. Cardiol 2002; 98: 154-8.
7. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, et al. Clinical factors associated with calcific aortic valve disease, Cardiovascular Health Study. J Am CollCardiol 1997; 29: 630-4.
8. Tolstrup K, Roldan CA, Qualls CR, Crawford MH. Aortic valve sclerosis, mitral annular calcium, and aortic root sclerosis as markers of atherosclerosis in men.Am J Cardiol 2002; 89: 1030-4.
9. Chandra HR, Goldstein JA, Choudhary N, O'Neill CS, George PB, Gangasani SR, *et al*. Adverse outcome in aortic sclerosis is associated with coronary artery disease and inflammation. J Am CollCardiol. 2004; 43: 169-75.
10. Akgün T, Tanboğa IH, Oduncu V, Kurt M, Cimen AO, Bitigen A. Reshaping the left Judkins catheter for a right coronary angiogram in the anomalous aortic origin of the right coronary: killing two birds with one left Judkins.Turk Kardiyol Dern Ars. 2012;40:513-7.
11. Principal Investigatiors of CASS and their Associaties.National Heart, Lung, and Blood Institute Coronary Artery Surgery Study. A multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981: 63 (6 pt 2): l1-8.
12. Hsu SY, Hsieh IC, Chang SH, Wen MS, Hung KC. Aortic valve sclerosis is an echocardiographic indicator of significant coronary disease in patients undergoing diagnostic coronary angiography.

Int J ClinPract 2005; 59:72-7.
13. Soydinc S, Davutoglu V, Dundar A, Aksoy M. Relationship between aortic valve sclerosis and the extent of coronary artery disease in patients undergoing diagnostic coronary angiography.Cardiol 2006; 106: 277-82.
14. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. Eur Heart J 1994 15: 865-70.
15. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors a causal relationship? A clinical morphologic study. ClinCardiol 1991c; 14: 995-9.
16. Deutscher S, Rockette HE, Krishnaswami V. Diabetes and hypercholesterolemia among patients with calcific aortic stenosis.J Chronic Dis 1984; 37: 407-15.
17. Lindroos M, Kupari M, Heikkila J, Tilvis R. Prevalence of aortic valve abnormalities in the elderly: an echocardiographic study of a random population sample. J Am CollCardiol 1993; 21: 1220-5.