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Association between Aortic Sclerosis and Coronary Artery Disease

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ABSTRACT

Background: Although there is a recognized link between cardiovascular hazards and coronary artery disease (CAD), it is still unknown whether aortic sclerosis and CAD are linked.

Objective: This study aimed to check whether if there is a link between aortic sclerosis and the existence and severity of coronary artery disease .

Patients and methods: 204 individuals were enrolled in the study, transthoracic echocardiographic, and coronary angiography were done. Aortic leaflets were tested for the amount of thickness in the short axis view. The involvement of coronary arteries represented by the gensini score and the association between aortic valve sclerosis score and the degree and severity of coronary affection was investigated using the Gensini score.

Results: The individuals were divided into 2 groups grounded on the severity of aortic valve sclerosis. Group A (GP A) included patients with aortic valve sclerosis (AVS) ≥ 2 and group B (GP B) included patients with AVS < 2. In GP A, the right coronary cusp was the most afflicted one, whereas the LAD was the most affected in coronaries. The degree and severity of CAD were more significant in GP A, as evidenced by a higher Gensini score value of 39.27 versus 28.84 in GP B.

Conclusion: AVS has been found to be correlated with the presence and severity of CAD and could be used as a potential surrogate marker for the illness.

Keywords: Aortic valve sclerosis (AVS), Coronary angiography, Coronary artery disease (CAD).

INTRODUCTION

Multiple research has described calcification or bright echoes in defining sclerosis [1, 2], with a peak Doppler velocity of 2.5 meters per second, [3] 2 meters per second [2], but the usage of Doppler in describing AVS is not yet widespread [5]. In symptomatic patients [3] and patients presenting with chest discomfort [1], some studies have shown a link between aortic sclerosis and cardiovascular events. Epidemiological studies suggest that AVS is associated with both all-cause and cardiovascular mortality, independently of age [3]. Because AVS does not generate hemodynamic changes that affect cardiovascular function, the mechanisms that underpin its link to poor cardiovascular outcomes remain unknown.[1]. Several studies have shown that more extensive calcifications in AVS, despite not having a hemodynamic effect, amplify the likelihood of CAD and cardiovascular events [4].

Independent risks for CAD as with dyslipidemia, hypertension, and male sex have been shown in several studies to influence aortic sclerosis and its progression to aortic stenosis [1].

The aim of the study was to see if there was an association between AVS with the presence and severity of CAD.

PATIENTS AND METHODS

Ethical approval:

The study was approved by the Ethics Board of Al-Azhar University and an informed written consent was taken from every participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association

(Declaration of Helsinki) for studies involving humans.

Study population: We have included 204 patients with suspected CAD, referred to the Cath Department, Menufia University Hospital for elective coronary angiogram for evaluation of CAD.

Exclusion criteria: Patients with aortic valve stenosis, or congenital valvular anomalies (bicuspid valve, supravalvular stenosis, subvalvular obstruction), or other primary valvular diseases, patients with chronic kidney disease or with poor echo window were also excluded.

All participants in the trial were subjected to complete medical history, as with the previous history of hypertension, diabetes mellitus, CAD, dyslipidemia, and CAD among the subject's families. They were also given a full physical examination and a 12-lead ECG.

Echocardiography:

A complete examination was performed (utilizing GE Vivid S5, Vivid E9 echocardiography equipment with 1.7–4MHz phased array transducers).

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Echocardiographic pictures were obtained from all standard viewpoints, and ejection fraction was recorded and calculated as per the American Society of Echocardiography's recommendations [6].

Echocardiogram evaluation of the aortic valve cusps was carried out from the parasternal long-axis (for right and noncoronary cusps) and parasternal short axis at the root of great vessels level. Echo-doppler assessment was done from multiple acoustic windows, including the apex, suprasternal notch. Patients with a peak velocity of more than 200 cm/sec. were excluded from our study [2, 3].

In the short-axis view, aortic leaflets were examined for the amount of thickness, according to **Chandra *et al.*** [7] zero for normal cusps; 1, mild (mild affection of one cusp); 2, moderate (mild affection of two cusps or severe affection of one cusp); and 3, severe (severe affection of two cusps or affection of all three cusps) [7].

Patients were divided into 2 groups as per their scores of aortic valve sclerosis: (1) GP A with AVS ≥ 2, (2) GP B with AVS < 2.

Coronary angiography:

All candidates were scanned using a Siemens machine. We employed the femoral approach for all patients, and numerous images were obtained. Images were taken with a digital camera. The Gensini score [9] was used to calculate the extent and severity of CAD. The principle of Gensini score is based upon assigning a number for a degree of constriction for coronary artery lumens (1, 2, 4, 8, 16, or 32), which is correlating to a reduction in blood flow (25 percent, 50 percent, 75 percent, 90 percent, 99 percent, and complete occlusion, respectively).

This score accounts for the functional importance of the area served by the diseased artery. For example, the Left main coronary artery (LM) gets a score of 5, while the proximal part of the left anterior descending coronary artery (LAD) gets a score of 2.5, and the mid-part of the LAD receives a score of 1.5. the apical part of LAD receives a score of 1. These areas were furtherly detailed in his study [9].

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level [10]. Chi-square test was used for categorical variables, to compare between different groups. F-test (ANOVA) was used for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (LSD) for pairwise comparisons. Kruskal Wallis test was used for abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons. Spearman coefficient was used to correlate between two distributed abnormally quantitative variables.

Receiver operating characteristic curve (ROC): It is generated by plotting sensitivity (TP) on Y axis versus 1-specificity (FP) on X axis at different cut off values. The area under the ROC curve denotes the diagnostic performance of the test. Area more than 50% gives acceptable performance and area about 100% is the best performance for the test. The ROC curve allows also a comparison of performance between two tests. Sensitivity is the capacity of the test to correctly identify diseased individuals in a population "TRUE POSITIVES". The greater the sensitivity, the smaller the number of unidentified cases "false negatives". Specificity is the capacity of the test to correctly exclude individuals who are free of the disease "TRUE NEGATIVES".

The greater the specificity, the fewer "false positives" will be included. Positive predictive value (PPV) is the probability of the disease being present, among those with positive diagnostic test results. Negative predictive value (NPV) is the probability that the disease was absent, among those whose diagnostic test results were negative. Accuracy: Rate of Agreement = (True positives + True negatives) / Total tested x 100.

RESULTS

The study enrolled 204 patients 194 males and 10 females. Mean age was 56.7 years. Hypertension was the most common risk factor representing 56.9 % of the population followed by dyslipidemia 55.4%. By echocardiography, right coronary cusp was the most affected cusp in 118 patients, sclerosis score was zero in 23 patients, while it was 1 in 52, 2 in 73, and was 3 in 56 patients. By coronary angiogram, LAD occlusion was the most affected present in 112 patients representing 55% of the population, patients with multivessel affection were representing 42%, whilst single vessel 48%, and mean Gensini score in all study population was 35.43 **(table 1)**

Table (1): Demographic data, risk factors, echocardiography and angiogram findings in the study population

Count (%)			204 (100%)
Male			194 (93.1%)
Female			9 (6.9%)
Mean age (years)			56.7 ± 8.6
DM	104		51.0%
HTN	116		56.9%
Smoking	101		49.5%
F/H	105		51.5%
Dyslipidemia	113		55.4%
RT cusp affection	118		57 %
Left cusp affection	89		43%
Non coronary cusp	75		36 %
Sclerosis score	0	23	11.3%
	1	52	25.5%
	2	73	35.8%
	3	56	27.5%
LMC	5		2.5%
LAD	112		54.9%
LCX	93		45.6%
Ramus	3		1.5%
RCA	73		35.8%
CAD	Multi vessels	86	42.2%
	Single	98	48.0%
	No	20	9.8%
gensini score			35.43

The study population was further divided into two groups based on their aortic valve sclerosis score (AVS). GP A included 129 patients with AVS ≥ 2, while GP B included 75 patients with AVS < 2. there was no significance regarding age and sex distribution. Diabetes and smoking were more frequent in group A, (P values were 0.007 and 0.038 respectively). As regards the distribution of coronary cusps, RCC was the most affected cusp, recorded in 70 patients in GP A, and in 48 patients in GP B, (P-value 0.05). Other cusps showed no significance. Anatomical distribution of coronary lesions showed LAD was the most affected artery, GP A contained 84 patients (65.1%), while GP B showed 28 patients (37.3%) with P-value < 0.001, other vessels showed no significance (Table 2).

Table (2): Demographic data, risk factors, Echocardiography and angiogram findings in both groups

Parameters		**Aortic valve sclerosis**				**P value**
		GP A ≥2		**GP B <2**		
		Mean	**SD**	**Mean**	**SD**	
Age (years)		56.95	8.04	56.15	8.75	0.504
Sex	**M**	121	93.8%	69	92.0%	0.624
	F	8	6.2%	6	8.0%	
DM		75	58.1%	29	38.7%	0.007
HTN		78	60.5%	38	50.7%	0.173
Smoking		71	55.0%	30	40.0%	0.038
F/H		72	55%	38	50.7%	0.861
Dyslipidemia		67	51.9%	46	61.3%	0.193
Right coronary cusp		70	54.3 %	48	70 %	0.05
Left coronary cusp		18	13 %	71	91.6%	0.21
Non coronary cusp		0	0	75	100	0.65
LMC		4	3.1%	1	1.3%	0.654
LAD		84	65.1%	28	37.3%	< 0.001
LCX		58	45.0%	35	46.7%	0.814
Ramus		2	1.6%	1	1.3%	1
RCA		42	32.6%	31	41.3%	0.207
Single vessels		59	45.7%	27	36.0%	0.23
Multivessels		59	45.7%	39	52.0%	0.36
Normal coronaries		11	8.5%	9	12.0%	0.11

Patients in GP A showed single coronary vessel affection in 45.7% of patients, multivessel affection in 45.7%**.** While, in GP B patients with single vessels were 52.0 %, multivessel 36.0%, with a P-value of 0.361. The mean Gensini score in GP A, was 39.27 ± 29.51, while in group B it was 28.84 ± 27.96 (the P-value was 0.005) as shown in table (3).

Table (3): Severity of CAD assessed using Gensini score in both groups

Parametrs	Aortic valve sclerosis										P value
	GP A					GP B					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Gensini score	39.27	29.51	36.00	0.00	112.00	28.84	27.96	22.00	0.00	120.00	0.005

Using multivariate analysis of independent factors for detection of Gensini score ≥ 34.5, LAD affection and aortic valve sclerosis were highly significant variables (P-value < 0.001). While aortic valve sclerosis ≥ 2 showed a P-value of 0.006, which was very significant as independent factors for prediction of higher Gensini score. **(table 5).** the predictive performance of AVS ≥ 2 for Gensini score ≥ 34.5, showed sensitivity of 53.5 %, specificity of 74.7 %, area under ROC of 0.619, and significance of 0.005 **(table 4).**

Table (4): The predictive performance of AVS score for Gensini score ≥ 34.5; ROC curve analysis

Area below the curve	P-value	95% CI		Cut off	Sensitivity %	Specificity %
		Lower	Upper			
0.619	0.005	0.540	0.698	34.5	53.5	74.7

Table (5): Multivariate analysis for Gensini score ≥ 34.5

Parameters		P value	OR	95% C.I.	
				Lower	Upper
Gensini>34.5	**Aortic valve sclerosis**	0.006	2.551	1.314	4.952
	LAD	<0.001	4.228	2.245	7.964

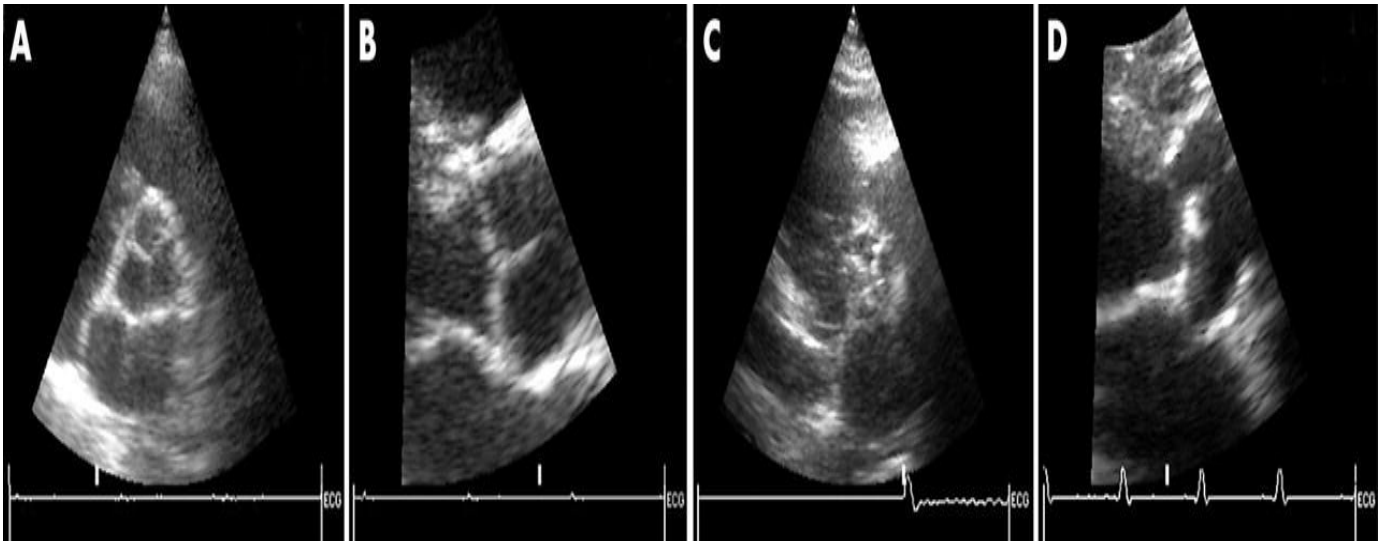

Figure (1): Echocardiography for AVS case. A) indicated standard cusps in the parasternal short axis, B) showed enlarged image in the parasternal long axis, while C) showed sclerotic cusps in the short axis, and D) showed sclerotic cusps in the long axis [8]

DISCUSSION

AVS is a condition that happens when cusps thicken and reflect more light on echocardiogram, although there is no indication of detrimental hemodynamic effects [1]. AVS is a common occurrence in various patient groups, and its incidence rises with age, with an estimated prevalence of 40% in people over 75 years old [11]. In symptomatic individuals and those who arrive with chest discomfort, some studies had shown a link between aortic sclerosis and cardiovascular events [1].

In our work, we found that there was a significant relation between aortic valve sclerosis and the severity of CAD (represented by Gensini score). As patients with AVS ≥ 2 had a mean Gensini score of 39.27, while those with AVS < 2 have a lower gensini score of 27.96 with a P-value of 0.005 and with a positive correlation between AVS and Gensini score value. Also, the predictive performance of AVS ≥ 2 for Gensini score 34.5 had a sensitivity of 53.5% and specificity of 75% with a P-value of 0.005. On multivariate analysis of independent factors for detection of Gensini score ≥34.5, LAD affection and aortic valve sclerosis showed significant variables, with P value < 0.001 and 0.006 respectively.

We found that diabetes and smoking were more prevalent risk factors in group A. This is in agreement with early studies, which showed a higher occurrence of traditional cardiovascular risk factors among patients with valve sclerosis [12]. The amplified cardiovascular hazards among AVS patients might be contributed by multiple mechanisms. AVS and CAD, both had equivalent risk factors for atherosclerosis. Additionally, AVS and CAD shared the same histopathological characteristics of atherosclerosis. furthermore, previous studies documented a strong direct association between AVS and atherosclerosis in different arterial districts [13]. Some hypothesis states that AVS could be an indicator of subclinical CAD. Supporting this hypothesis, what has been found for the association between AVS, atherosclerosis of the aorta, and the fact that around 65% of patients undergoing aortic valve replacement (TAVR) had simultaneously significant CAD [14]. Other theories propose that aortic sclerosis is defined at the tissue level by isolated patches of subendothelial thickening on the aortic side of the valve cusps. Although there is no clear evidence for this concept, endothelial breakdown caused by shear stress on the aortic side of the leaflet is thought to be the cause of the disease [15]. **Soydinc *et al.*** [16] found that individuals with AVS had a higher Gensini score (40.7 ± 38.05 vs. 18 ± 16.4; p 0.001). On multivariate analysis age (p < 0.001), male sex, and Gensini score (p = 0.003) were found as independent predictors of AVS. **Hisar *et al.*** [17] found that detection of AVS by echocardiography could be a beneficial non-invasive tool for identification of CAD in patients aged below 75 years. It was also found that patients with CAD had higher rates of aortic valve calcifications than those without CAD (44% versus 26%, p = 0.005). [18] Similarly, the rates of aortic valve calcifications were also raised in subjects with elevated Gensini scores than in those with a minimum score. Other remarks were also demonstrated when AVS existence was considered as an important independent predictor to demonstrate the complexity of CAD. Additionally, AVS has a significant correlation with SYNTAX scores. However, the role of AVS was not statistically correlated with the acute coronary syndrome.[19]

On the other hand, **Hemal Bhatt *et al.*** [20] found that on multivariate regression analysis only age was independently associated with the presence of AVS.

Although, univariate analysis showed a significant relation between AVS and the existence of CAD, number of coronary vessels affection and calcification of the lesion that was near significant relation with Syntax score. The limitation of the above study is that they classified patients into two groups based on visual presence or absence of sclerosis, without considering its severity. Also, it was a retrospective study and this means that Echo interpretation was not limited to fewer cardiologists and interobserver variability cannot be neglected.

The study had some limitations that should be addressed in further studies. In our study, we included only small numbers of patients. Additionally, echogenicity was depending on observer eyeball with inter-and intra-observers variability. Another issue was related to CAD evaluation, as it depends on the anatomical site and extent of the lesion, not considering other variables such as the existence of collaterals, bifurcation, trifurcation, calcifications and tortuosity of the lesions.

CONCLUSION

From the present work, we concluded that AVS could be related to the existence and severity of CAD and can represent a potential hazard for CAD.

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