

Aortic stenosis calcium scoring in a racially mixed sample

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Abstract

Aortic stenosis (AS) is common and increasing in prevalence as the population ages. Using computed tomography (CT) to quantify aortic valve calcification (AVC) it has been reported that men have greater degrees of calcification than women among subjects with severe AS. These data, however, were derived in largely Caucasian populations and have not been verified in non-Caucasian subjects. This retrospective study identified 137 patients with severe AS who underwent valve replacement and had CT scans within 6 months prior to surgery. AVC scores were compared between men and women, both in the entire sample and in racial subgroups. 52% of subjects were male and 62.8% were non-Caucasian. Mean AVC score for the entire cohort was 3062.08±2097.87 with a range of 428-

13,089. Gender differences in aortic valve calcification were found to be statistically significant with an average AVC score of 3646±2422 in men and 2433±1453 in women (p=0.001). On multivariate analysis, gender remained significantly associated with AVC score both in the entire sample (p=0.014) and in the non-Caucasian subgroup (p=0.008). Mean AVA was significantly greater in males than females but this difference disappeared when AVA was indexed to BSA (p=0.719). AVA was not different between racial groups (p=0.369). In this research we observed that among subjects with severe AS men have higher AVC scores than women regardless of racial background. This is consistent with previous studies in predominantly Caucasian populations.

Introduction

Aortic stenosis (AS) is a major public health problem with rising incidence and prevalence as the population ages [1-3]. The standard way to diagnose AS is with echocardiography. However, in certain situations, particularly “low-flow low-gradient” AS, it can be difficult to distinguish between true severe AS and “pseudo-severe” AS [4]. To resolve this difficulty, it has been suggested that calcium scoring by computed tomography (CT) scan can reliably determine the presence or absence of severe AS [5,6]. A key caveat is that threshold calcium scores differ between men and women. These thresholds were derived from a largely Caucasian population and have not been verified in non-Caucasian subjects [7].

In previous work looking at calcium scores in a broad sample of in- and out-patients with clinically indicated chest CTs (not limited to AS), we also observed gender differences in degree of aortic valve calcification (AVC). However, this was true only among Caucasian subjects [8]. We therefore undertook the current study to test the hypothesis that the gender difference in degree of calcification among subjects with severe AS would be present in Caucasian subjects but not others.

Methods

Retrospective chart review was performed to identify subjects with a history of surgical aortic valve replacement/repair between 2007 and 2015. Severity of aortic valve stenosis was defined using standard recommendations for echocardiographic assessment of aortic valve stenosis. Both subjects with classical severe aortic stenosis as well as those with low flow-low gradient severe aortic stenosis were included. Clinical judgment was applied for subjects who do not meet standard criteria for severe aortic stenosis. 164 patients were initially identified. Of these 137 had a CT scan within

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Ethics approval: This retrospective chart review study was approved by the Institutional Review Board of the Einstein Healthcare Network.

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Key words: Aortic valve calcium; severe aortic stenosis; computed tomography; gender differences.

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six months of valve replacement; they form the study sample. CT scans were performed for various clinical reasons in both the inpatient and outpatient setting. Demographic and clinical data were collected for each patient from electronic medical records. These included age, gender, ethnicity, body mass index, body surface area, blood pressure, heart rate, symptoms, New York Heart Association (NYHA) function class, history of coronary artery disease (CAD), hypertension (HTN), dyslipidemia, diabetes mellitus (DM), body surface area (BSA), kidney disease, and smoking status. Echocardiographic data were also collected including: aortic valve morphology, maximal velocity, VTI, peak and mean gradient, and area (by continuity equation); left ventricular outflow tract (LVOT) diameter, area, VTI, and maximum velocity; stroke volume; left ventricular ejection fraction (LVEF), and aortic dimensions (sinus of Valsalva, sinotubular junction and ascending aorta diameters). We also obtained dimensions of the interventricular septum, left ventricular posterior wall, left ventricular inner dimension in both systole and diastole, and presence (and degree) of aortic, mitral, and tricuspid valve regurgitation.

The CT examinations were performed using Brilliance iCT, (Philips Healthcare, Cleveland, OH, USA) or LightSpeed VCT (General Electric Healthcare, Milwaukee, WI, USA) scanners. Thin slices of 0.62 mm and 1.25 mm were generated, and images were examined utilizing a Synapse PACS system (Fujifilm Medical Systems, USA Inc.). Routine CT scans of the chest as well as ECG gated examinations for coronary calcium score were accepted for AVC analysis (Figure 1). This was conducted either manually or with the help of automatic software (IntelliSpace, Philips Healthcare). With the manual processing, the boundaries of each calcification were carefully delineated with calculation of the area (in mm²) and CT density (in Hounsfield units) for each slice containing a calcification. Multiplication of these values yielded the AVC score [9]. There was a strong correlation ($r=0.89$) of the scores obtained from the automatic software and manually. The same method was applied for evaluation of mitral valve apparatus calcification (MVC).

The prevalence and density of AVC and MVC scores across race and gender were assessed. Data are presented as mean and standard deviation for continuous variables, and numbers and percentages

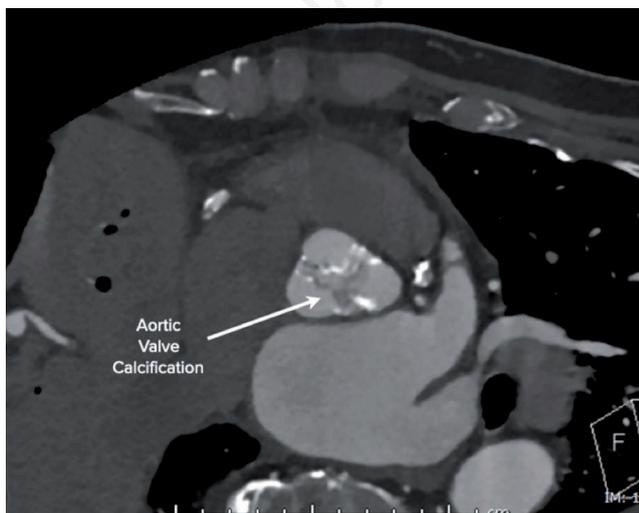


Figure 1. Cardiac computed tomography showing aortic valve calcification (AVC).

for categorical variables. We compared AVC and MVC scores between men and women in i) the entire cohort, ii) non-Caucasian subjects, and iii) Caucasian subjects. As variances were roughly equally distributed, we used Student's *t*-test for these analyses. Nonparametric correlation (Spearman) was used to assess associations between AVC score and continuous variables (age, BSA, BMI). To test for an independent association between gender and AVC score we performed multivariate analysis controlling for various confounders (age, race, BSA, DM, HTN and CAD). A 2-tailed *p*-value of <0.05 was statistically significant. Statistical analyses were performed using JMP, version 11.0 (SAS Institute, Cary, North Carolina). This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Institutional Review Board of the Albert Einstein Healthcare Network.

Results

The study included 137 subjects. Baseline characteristics are shown in Table 1. Half were male (52%) and the majority were non-Caucasians (62.8%). Among non-Caucasian subjects all but 11 were African American. Thus, separate analyses for specific racial groups were not performed. Hypertension was the most common comorbidity followed by hyperlipidemia, diabetes mellitus and COPD respectively. Mean aortic valve area (AVA) was significantly different between men and women; 0.80 ± 0.19 cm² vs 0.72 ± 0.18 cm²; $p=0.026$. However, this difference disappeared when AVA was indexed to BSA ($p=0.719$). Mean AVA was similar between Caucasian and non-Caucasian subjects; 0.76 ± 0.21 cm² vs 0.76 ± 0.18 cm²; $p=0.984$. There were also no significant differences between Caucasian and non-Caucasian subjects when AVA was indexed to BSA ($p=0.369$).

The mean AVC score for the entire cohort was 3062.08 ± 2097.87 with a range of 428-13,089. There were no significant differences in the mean AVC score between Caucasian and non-Caucasian subjects: 3315 ± 2323 vs 2911 ± 1951 , $p=0.278$. However, gender differences in aortic valve calcification were found to be statistically significant with an average AVC score of 3646 ± 2422 in men and 2433 ± 1453 in women ($p=0.001$). We also analyzed our cohort according to previously published, gender-specific cutoffs for AVC score [6,10]. 102 of our 137 subjects (74%) met the suggested "best" thresholds for determining the presence of severe aortic stenosis (1274 in women and 2065 in men). One hundred and eighteen (118) subjects (86%) met a more liberal threshold (791 in women and 1661 in men) chosen to include 95% of subjects in the referenced study [6].

In non-Caucasian patients ($n=86$) gender differences in AVC score were present and statistically significant (3577.84 ± 2342.81 in men vs 2384.75 ± 1384.95 in women, $p=0.004$, Table 2). Among Caucasian patients ($n=51$) AVC scores were similarly different in males compared to females though the difference did not reach statistical significance (3724.67 ± 2546.12 vs 2564.72 ± 1659.11 , $p=0.089$), possibly because of smaller sample size. Similar results were obtained when AVC score was indexed to BSA.

In comparisons of AVC score with various demographic and clinical variables, significant associations were found for gender ($p=0.002$), BSA ($p=0.008$), bisphosphonate use ($p=0.012$) and insulin use ($p=0.031$). On multivariate analysis, after controlling for age, race, BSA, CKD, DM, HTN and smoking history, gender remained significantly associated with AVC score ($p=0.014$). Interestingly, Bisphosphonate use was also found to be significantly associated with AVC score (Table 3) but only 4 subjects were taking

bisphosphonates. When only the non-Caucasian subgroup was examined, gender was still significantly associated with AVC score ($p=0.008$).

Eighty-two patients had data available for mitral valve Agatston calcium score (MVC). The mean MVC score for the entire cohort was 1600.53 ± 2810.94 with a range of 10.54-19726. There were

Table 1. Baseline demographic and echocardiographic variables.

n (%), mean \pm SD	Males (n=71) 52%	Females (n=66) 48%	p value	n (%), mean \pm SD	Males (n=71) 52%	Females (n=66) 48%	p value
Age	75.22 \pm 9.89	79.69 \pm 11.35	0.015	Echocardiographic data			
Ethnicity				Aortic valve morphology			
Caucasian	33 (46.5%)	18 (27.3%)	0.025	Tricuspid	47 (66.2%)	53 (81.5%)	0.08
African American	36 (50.7%)	39 (59.1%)		Bicuspid	2 (2.8%)	0	
Hispanic	2 (2.8%)	6 (9.1%)		Unknown	22 (31%)	12 (18.5%)	
Others	0	3 (4.5%)		LVOT diameter (mm)	1.98 \pm 0.16	1.90 \pm 0.15	0.003
Body surface area	1.98 \pm 0.23	1.79 \pm 0.24	<0.0001	LVOT area (cm ²)	3.09 \pm 0.51	2.85 \pm 0.44	0.003
Body mass index	26.53 \pm 6.06	28.7 \pm 7.6	0.066	LVOT VTI (cm)	20.21 \pm 6.5	21.34 \pm 6.42	0.310
New York Heart Assoc. Class				LVOT Vmax (cm/s)	94.1 \pm 27.56	97.67 \pm 23.94	0.420
I	13 (18.3%)	12 (18.2%)	0.572	Stroke volume	61.24 \pm 18.16	60.19 \pm 18.89	0.741
II	11 (15.5%)	16 (24.2%)		Stroke volume index	31.35 \pm 9.99	33.98 \pm 10.64	0.137
III	31 (43.7%)	23 (34.8%)		Aortic valve Vmax (cm/s)	367.73 \pm 76.70	387.14 \pm 78.64	0.068
IV	16 (22.5%)	15 (22.7%)		Aortic Valve VTI (cm)	79.23 \pm 20.26	85.51 \pm 25.82	0.114
Hypertension	62 (87.3%)	59 (89.4%)	0.794	Peak gradient (mmHg)	58.37 \pm 20.53	65.05 \pm 24.71	0.087
Dyslipidemia	48 (67.6%)	44 (66.7%)	1.000	Mean gradient (mmHg)	34.97 \pm 13.1	38.59 \pm 15.97	0.148
Diabetes	32 (45.1%)	29 (43.9%)	1.000	AVA (cm ²)	0.80 \pm 0.19	0.72 \pm 0.18	0.026
COPD	20 (28.2%)	20 (30.3%)	0.852	AVA calculated (cm ²)	0.79 \pm 0.19	0.73 \pm 0.19	0.062
History of smoking	22 (31%)	15 (22.7%)	0.337	AVAi	0.41 \pm 0.10	0.42 \pm 0.11	0.719
CKD stage 3 and above	27 (38%)	20 (30%)	0.372	AVAi calculated	0.40 \pm 0.10	0.41 \pm 0.11	0.747
Previous myocardial infarct	34 (47.9%)	25 (37.9%)	0.300	Ao Valsalva sinus diameter	31.08 \pm 5.18	28.21 \pm 4.09	<0.0001
Previous bypass surgery	8 (11.3%)	6 (9.1%)	0.781	Ao STJ diameter (mm)	25.17 \pm 4.43	22.8 \pm 3.63	<0.0001
Previous PCI	48 (67.6%)	41 (62.1%)	0.591	Ao Ascending diameter (mm)	31.0 \pm 5.2	28.73 \pm 4.67	0.008
Medications				IVSd (mm)	12.13 \pm 2.48	12.54 \pm 3.08	0.384
ACEi	30 (42.3%)	19 (28.8%)	0.111	IVSs (mm)	16.8 \pm 3.28	17.67 \pm 3.92	0.163
ARB	3 (4.2%)	5 (7.6%)	0.481	LVPWd (mm)	12.06 \pm 2.58	12.21 \pm 2.38	0.727
Beta blocker	47 (66.2%)	41 (62.1%)	0.722	LVPWs (mm)	17.39 \pm 3.28	17.47 \pm 3.63	0.899
Calcium channel blocker	15 (21.1%)	18 (27.7%)	0.426	Lvd (mm)	46.75 \pm 8.73	43.35 \pm 7.01	0.014
Diuretics	29 (40.8%)	30 (45.5%)	0.608	LVs (mm)	34.25 \pm 9.35	28.24 \pm 8.32	<0.0001
Statins	48 (67.6%)	47 (72.3%)	0.580	LVEF (%)	47.79 \pm 15.23	55.91 \pm 12.73	0.001
Other antilipids	4 (5.6%)	2 (3.1%)	0.682	Aortic regurgitation			
Oral hypoglycemics	3 (4.2%)	5 (7.7%)	0.479	None/trace	41 (57.7%)	38 (57.6%)	0.691
Insulin	28 (39.4%)	19 (28.8%)	0.211	Mild	20 (28.2%)	20 (30.3%)	
Antiplatelets	48 (67.6%)	45 (68.2%)	1.000	Moderate	10 (14.1%)	7 (10.6%)	
Anticoagulants	13 (18.3%)	10 (15.2%)	0.654	Severe	0	1 (1.5%)	
Bisphosphonates	2 (2.8%)	2 (3%)	1.000	Mitral regurgitation			
Calcium	5 (7%)	10 (15.2%)	0.173	None/trace	35 (49.3%)	35 (53%)	0.588
Vitamin D	9 (12.7%)	14 (21.2%)	0.253	Mild	27 (38%)	20 (30.3%)	
				Moderate	9 (12.7%)	11 (16.7%)	
				Severe	0	0	
				Tricuspid regurgitation			
				None/trace	45 (63.4%)	34 (51.5%)	0.393
				Mild	17 (23.9%)	17 (25.8%)	
				Moderate	8 (11.3%)	14 (21.2%)	
				Severe	1 (1.4%)	1 (1.5%)	
				Mitral Agatston score	1636.11 \pm 3768.79	1578.90 \pm 2068.01	0.929
				Aortic Agatston score	3646.09 \pm 2422.84	2433.83 \pm 1453.74	<0.0001

COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVOT, left ventricular outflow tract; VTI-velocity time integral; Vmax-maximum velocity; AVA, aortic valve area; AVAi, aortic valve area index; Ao, aortic; STJ, sinotubular junction; IVSd, Interventricular septal end diastole and end systole (IVSs); LVPWd, Left ventricular posterior wall thickness at end -diastole; end systole (LVPWs); Lvd, left ventricular diameter diastole; LVs, left ventricular diameter systole; LVEF, left ventricular ejection fraction.

Table 2. Comparison of mean aortic Agatston score between gender and ethnic groups.

	Male (n=71)	Female (n=66)	p value
Caucasian	3724.67 \pm 2546.12 (n=33)	2564.72 \pm 1659.11 (n=18)	0.089
Non-Caucasian	3670.22 \pm 2303.90 (n=37)	2384.75 \pm 1384.95 (n=48)	0.002
p value	0.801	0.658	

significant differences in the mean MVC score between Caucasian and non-Caucasians 2726.62 ± 3973.67 vs 802.88 ± 981.59 ($p=0.02$). This was apparent even in analysis of Caucasian females vs non-Caucasian females ($p=0.0001$) but was not present in males ($p=0.189$, Table 4). In contrast to the AVC findings above, no gender differences independent of ethnicity in mitral valve calcification were found with mean MVC score of 1636.11 ± 3768.79 in men and 1578.90 ± 2068.01 in women ($p=0.929$). In non-Caucasian patients ($n=48$) MVC score was lower in males than in females but this was not statistically significant ($p=0.484$, Table 4). Among Caucasian patients ($n=34$) MVC scores were also lower in males compared to

females but the difference was not statistically significant ($p=0.693$, Table 4). On correlational analysis, MVC was associated with race ($p=0.008$) alone. With multivariate regression, only race was significantly associated with MVC ($p=0.003$) (Table 5).

Discussion

Calcium load in the stenotic aortic valve can be precisely quantitated by multi-detector CT. The resultant AVC scores have

Table 3. Multivariate regression on factors associated with aortic valve Agatston score.

Variable	Beta	95% Confidence interval	p value
Age <i>Referrant</i>	-13.58	-47.83 to 20.68	0.434
Female <i>Referrant</i>	-930.43	-1668.68 to -192.20	0.014
African American	-7.38	-722.13 to 707.37	0.984
Hispanic	155.11	-1387.08 to 1697.30	0.843
Others	-386.69	-2744.89 to 1971.61	0.746
Body surface area	1522.14	34.15 to 3010.13	0.045
Diabetes	-644.30	-1463.03 to 174.43	0.122
Hypertension	-299.06	-1381.81 to 783.69	0.586
Smoking history	7.09	-771.82 to 786	0.986
Chronic kidney disease	-296.34	-1013.21 to 420.53	0.415
Bisphosphonates use	3481.23	1488.61 to 5473.84	0.001
Insulin use	-416.76	-1228.95 to 395.43	0.312

Table 4. Comparison of mean mitral Agatston score between gender and ethnic groups.

	Male (n=31)	Female (n=51)	p value
Caucasian	2451.20 ± 4940.04 (n=17)	3002.05 ± 2828.72 (n=17)	0.693
Non-Caucasian	646.36 ± 907.73 (n=14)	867.33 ± 1017.42 (n=34)	0.484
p value	0.189	0.0001	

Table 5. Multivariate regression on factors associated with mitral valve Agatston score.

Variable	Beta	95% Confidence interval	p value
Age <i>Referrant</i>	19.08	-40.27 to 78.42	0.523
Female <i>Referrant</i>	755.79	-680.52 to 2192.1	0.298
African American	-2054.57	-3373.95 to -735.19	0.003
Hispanic	-2260.63	-5353.97 to 832.702	0.149
Others	-2393.42	-5802.79 to 1015.95	0.166
Body surface area	2081.86	-1115.39 to 5279.12	0.198
Diabetes	1414.62	-114.63 to 2943.86	0.069
Hypertension	-1730.52	-3953.49 to 492.46	0.125
Smoking history	-0.825	-1447.24 to 1445.59	0.999
Chronic kidney disease	365.39	-976.45 to 1707.23	0.589
Bisphosphonates use	-911.68	-4143.98 to 2320.63	0.575
Insulin use	-1367.90	-2869.49 to 133.70	0.0740

been correlated with the weight of valves excised at the time of surgery [10], and have prognostic value [11]. Recent work has shown that, for the same degree of stenosis, men and women have differing calcium burdens. This has led to the proposal of gender-specific cutoffs for identification of severe AS [6]. CT measurement of calcium burden can be particularly useful in assessing AS severity when stroke volume is reduced and transvalvular gradients are low [7]. However, these studies have all involved predominantly Caucasian subjects. To our knowledge, the current research is the first to extend these observations to a racially diverse population.

Calcification of the aortic valve occurs at early stages of the disease, characterized by an active inflammatory process that shares similarities with atherosclerosis [12]. The association between accumulation of calcium and severity of AS has been amply demonstrated both by autopsy and CT. Aggarwal *et al.* were the first to convincingly demonstrate differences in AVC load between men and women with aortic stenosis [7]. While these differences were minimal at earlier stages of the disease, they became greater as disease severity increased. Further, differences in degree of valvular calcification remained after normalization for body surface area and cross-sectional area of the aortic annulus. While the pathophysiology behind these differences remains unclear, there are other examples of gender differences in various cardiac disease states. For instance, it has been noted that men have greater degrees of coronary artery calcification than women [13]. Additionally, there are gender differences in adaptation of the left ventricle to aortic stenosis [14,15] and patterns of hypertrophy [16,17] differ between the genders. In the case of calcific aortic stenosis, it has been postulated that women have greater degrees of valvular fibrosis and less intense calcification of the valve as compared to men [7].

We previously investigated differences in pattern and degree of cardiac calcification between men and women, and different racial groups [8]. Looking at subjects with any degree of AVC (as opposed to the current study which focused only on subjects with severe AS) we observed higher AVC scores in men versus women, but only among Caucasian subjects. Non-Caucasian subjects showed similar degrees of AVC in men and women. Based on this we hypothesized that the published gender-specific calcium thresholds for determination of severe AS [6] might only apply to Caucasian patients. The current findings refute that hypothesis. Severe AS appears to occur at lower calcium scores in women versus men regardless of race.

This work was retrospective and is subject to all the associated limitations. However, it reflects a diverse patient sample including a large number of women and minority patients, similar to what is encountered in many urban settings. This study was not designed to detect a cut-off value for severe AS. That would require studying a large series of patients with varying degrees of AS. Rather, we measured calcium scores in patients determined to have severe AS (as indicated by the need for valve replacement) and compared those scores between Caucasian subjects (for whom cutoffs have been determined) and non-Caucasian subjects. In addition, our patients fell largely within previously validated ranges of AVC score that have been associated with severe AS. While our sample size is not large enough to confirm published gender-specific thresholds, our results are consistent with them.

In conclusion, among subjects with severe AS men have a higher calcium burden than women for the same severity of stenosis. This difference occurs among non-Caucasian as well as Caucasian subjects.

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