

Research Article

Aortic Valve Calcium Score as an Adjunct for the Diagnosis of Aortic Stenosis Optimizing the Test

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Keywords

- Aortic valve calcification
- Aortic Stenosis
- Agatston method
- Low flow – low gradient Aortic Stenosis

Abstract

Purpose: To determine the optimal approach for measuring aortic valve calcification (AVC) on CT scan for the diagnosis of severe aortic stenosis (AS) as assessed by transthoracic echocardiogram (TTE).

Methods: We retrospectively studied 84 patients with mild to severe AS who underwent TTE and multi detector gated x-ray computed tomography (MDCT) for coronary calcium scoring. Aortic valve calcium was scored independently and relationships between TTE severity of AS and AVC were identified. Linear regression modeling was performed with aortic valve stenosis as the independent variable, and various aortic calcium scoring methods as predictors.

Results: There was good correlation between AVC and TTE mean gradient ($r=0.66$, $p<0.0001$), peak velocity ($r=0.60$, $p<0.0001$), and valve area ($r=-0.47$, $p<0.001$). The Agatston method for scoring AVC performed as well or better in predicting severe aortic stenosis than aortic valve calcium volume and aortic valve calcium mass scores. There was no improvement in the predictive model after indexing for aortic valve size or body size. A score of 1850 AU captured 96% of patients with severe aortic stenosis ($iAVA < .6 \text{ cm}^2 / \text{m}^2$) and 20/22 (90%) of patients with low gradient, severe aortic stenosis ($iAVA < .6 \text{ cm}^2 / \text{m}^2$ and mean gradient $< 40 \text{ mm hg}$).

Conclusion: Aortic valve calcium assessed on MDCT correlates reasonably well with aortic stenosis by echo. The use of the straightforward Agatston method for scoring without indexing appears to be the optimal approach. Aortic valve calcium scoring may be a particularly attractive modality for aiding the diagnosis in the subgroup of patients with low gradient, severe aortic stenosis.

INTRODUCTION

Acquired aortic stenosis (AS) is usually an idiopathic disease resulting from degeneration and calcification of the aortic leaflets [1,2]. AS is the most common valvular heart disease in developed countries and its prevalence is expected to increase due to the aging population [3]. A reliable and precise assessment of aortic stenosis severity is crucial for proper therapeutic management.

Transthoracic echocardiogram is the standard diagnostic test in the evaluation of patients with known or suspected aortic stenosis [4]. The stages and hemodynamic severity of AS is characterized by the TTE measurements of the transthoracic maximum velocity, mean pressure gradient and aortic valve area calculated through the continuity equation [4,5]. Doppler evaluation of severity of AS has been well validated in experimental and human studies with direct measurements of intracardiac pressures and cardiac output [6]. However, due to technical challenges, Doppler may underestimate or overestimate aortic valve velocity and disease severity in patients with poor

echocardiographic windows such as obese patients or those with severe chronic obstructive pulmonary disease. Echocardiography also has limitations in the presence of arrhythmia or concomitant aortic regurgitation [7]. In addition, Doppler echocardiography has limitations in the assessment of AS severity in patients with depressed left ventricular ejection fraction (EF) and low-flow - low-gradient (LF-LG) aortic stenosis [8]. Gradients are a squared function of flow, and even a modest decrease in flow may lead to an important reduction in gradient, even if the stenosis is very severe [9]. LF-LG severe AS related to a decrease in left ventricular ejection fraction (LVEF), may be observed in approximately 5% to 10% of patients with severe AS [10,11]. LF-LG severe AS may also be seen in patients with normal LVEF if forward flow is diminished, for example, in the setting of severe left ventricular hypertrophy. (9) Multi detector cardiac computed tomography (MDCT) has the ability to identify even small deposits of calcium and is widely used for non-invasive quantification of coronary artery calcium score (CACs) [12,13]. Aortic valve calcification is a primary process leading to aortic valve stenosis, and prior

studies have validated MDCT as an adjunct diagnostic modality to evaluate the AS severity [14,15]. The aim of our study was to analyze the optimal approach for measuring aortic valve calcification (AVC) using gated, non-contrast x-ray CT scanning to help aid the diagnosis of severe aortic stenosis (AS).

METHODS

This study was reviewed and approved by the Institutional Review Board of Saint Luke' Health System, Kansas City, MO. A total of 84 patients were selected from the database of Saint Luke's Mid America Heart Institute from the year 2000 to August, 2014. These patients had a diagnosis of mild to severe aortic stenosis and had undergone clinically indicated transthoracic echocardiograms and gated multi detector CT scans for coronary calcium scoring within 6 months of each other. We excluded patients with previous aortic valve replacement. Data extracted from the echocardiograms was used to determine the mean gradients across the aortic valves, peak aortic valve velocities, aortic valve area, and left ventricular ejection fraction.

To account for variability in body habitus, indexed aortic valve area (iAVA) was used in addition to traditional valve area. iAVA was calculated by dividing the aortic valve area by the individual's body surface area. Patients were then categorized as having mild, moderate and severe aortic stenosis (AS) based on the traditional and indexed valve areas [4]. Based on traditional valve area, mild AS was defined as $> 1.5 \text{ cm}^2$, moderate AS = $1.5 - 1.0 \text{ cm}^2$ and severe AS as $< 1.0 \text{ cm}^2$. According to indexed valve area, mild AS was defined as $> .85 \text{ cm}^2/\text{m}^2$, moderate AS = $0.85 - 0.6 \text{ cm}^2/\text{m}^2$ and severe AS as $< 0.6 \text{ cm}^2/\text{m}^2$. An aortic valve mean gradient of greater than 40 mm Hg was used as the cut off for high gradient.

Gated CT scans were performed utilizing a 16 or 64 slice multidetector scanner with field of view from the carina to the diaphragm to visualize the entire heart. CT settings were: 250 ms exposure, 2.5 mm slice thickness, 120 kVp, 40 mA and prospective triggering. Breath-hold instructions were used to minimize respiratory motion artifact and misregistration. The mean dose of radiation with each CT scan was 1-2 millisieverts (mSv). The images from this non-contrast, gated CT scans were analyzed to determine the aortic valve calcium scores using software application, *Syngo MMWP VE36A* (from Siemens Corp, Erlangen, Germany). This software allows visualization and quantification of calcified aortic valve areas with option of 3D editing for separation and modification of lesions within a defined volume. Using this software, three calcium scores were computed to determine the aortic valve calcification; Agatston score, calcium mass score, and calcium volume score. To account for inter-observer variability, two different observers independently calculated calcium scores.

Prior to actually scoring the valve calcium, the CT images of the aortic valve, subaortic space and proximal aorta were inspected in 3 dimensions. Calcification in the adjacent wall of the aorta and sub-aortic valve region were not included in the calcium score. The two readers reviewed this methodology together prior to scoring the valves independently.

STATISTICAL DESIGN

To determine which aortic calcium scoring method most

closely correlated with echocardiographic measures of severe aortic valve stenosis, we analyzed Spearman's correlations between three scoring methods (Agatston score, calcium mass score, and calcium volume score) and 1) aortic valve areas, 2) indexed aortic valve areas 3) mean gradients, and 4) peak velocities. Spearman's rho correlations were performed due to the non-normal distribution of the data. To determine the optimal method for measuring aortic valve calcification in patients with aortic stenosis, linear regression modeling was performed with aortic valve stenosis (iAVA) as the independent variable, and the three calcium scoring methods as predictors. To determine the sensitivity and specificity of using calcium scoring methods as a measure of aortic stenosis severity, we subjected the calculated Agatston scores, calcium mass scores and calcium volume scores to a receiver operating characteristic (ROC) curve, both at baseline and following indexing for CT sinotubular junction diameter (a convenient surrogate for aortic annulus) and body weight. The area under each ROC curve was measured using C-statistic.

PSS Suite statistical software, version 11.5 (SPSS Inc, Chicago, Ill) was used for data management.

RESULTS

Descriptive statistics

The basic demographics are summarized in Table (1). The mean age of the study population was 73.6 years, and 52 % were men. The severity of aortic stenosis in the 84 subjects varied from mild to very severe with a valve area range of 2.0 cm^2 to 0.3 cm^2 (median 1.1 cm^2). The average body surface area was 2.01 m^2 . 31/84 (37%) patients fulfilled the classic criteria of severe aortic stenosis as defined in the ACC/AHA Updated Valve guidelines ($V_{\text{max}} \geq 4\text{m/s}$ $\Delta P \geq \text{mean } 40$ and mm Hg) [4]. While 22 patients (26%) were deemed to have LF-LG s severe stenosis.

Correlation statistics

All three aortic valve calcium scoring systems (i.e., Agatston score, calcium mass score, and calcium volume score) significantly correlated with all 4 hemodynamic parameters of AS severity (i.e., non-indexed aortic valve area, indexed aortic valve area,

Table 1: Baseline population characteristics.

Demographic data	Mean	Range	Fraction (Subset/Total)
1 Age (years)	73.3	46- 96	
2 Male Gender			44/84
4 Atrial Fibrillation			20/84
5 Tobacco Usage			21/84
3 Body Mass Index	29.8	18.5- 49.9	
Aortic stenosis characteristics			
1 Ejection Fraction	64	29- 76	
2 Aortic Valve Area	1.141	0.3 - 2	
3 Peak gradient	38.13	17 - 102	
4 Mean gradient	21.81	0.7 - 64	
5 Calcium Score (Agatston method)	1384.31	3.2 - 8761.2	

mean gradient, and peak aortic valve velocity). We observed an inverse relationship between aortic valve calcium score (using all three scoring methods) and valve area, whereby calcium score increased with decreasing aortic valve area. In contrast, valve calcium scores positively correlated with mean gradient and peak aortic valve velocity - the higher the calcium score, the larger the mean gradient and higher the peak aortic valve velocity.

Determining the optimal method for diagnosing aortic stenosis severity

A linear regression using the three assessments of aortic valve calcium (Agatston score, calcium mass score, and calcium volume score) to predict aortic stenosis (iAVA) revealed a highly significant overall model ($F(3,79) = 12.007, p < .001; R^2 = .316$). Of these three calcium scoring methods, the Agatston scoring method was a unique significant predictor (Agatston: $t(82) = 2.195, p = .031, \beta = -1.327$; calcium volume: $t(82) = -.553, p = .582, \beta = -.114$; calcium mass: $t(82) = 1.744, p = .085, \beta = .917$). These statistics suggest that over and above calcium mass and calcium volume scoring systems, Agatston system correlated very well with aortic valve area (iAVA).

Quantifying the sensitivity and specificity of calcium scoring methods

Receiver operating characteristic (ROC) curves (Figure 1) analyzing the various approaches to calcium scoring as a valid test for classifying echocardiographic severity of aortic stenosis (state variable: severe stenosis determined through indexed iAVA. (Table 2) revealed that all calcium scoring systems excelled in identifying if a patient was classified as having severe aortic stenosis (area under curve [C-statistics] can be observed in Table 3). Thirty-seven ($n=37$) patients were classified as having "severe" aortic stenosis, while forty-five ($n=45$) patients were classified as having "not severe" aortic stenosis.

For all calcium scoring systems, the C-statistics fell within a confidence interval range of about .6 to .8. In particular, the upper bound of this range for the Agatston score method approached a

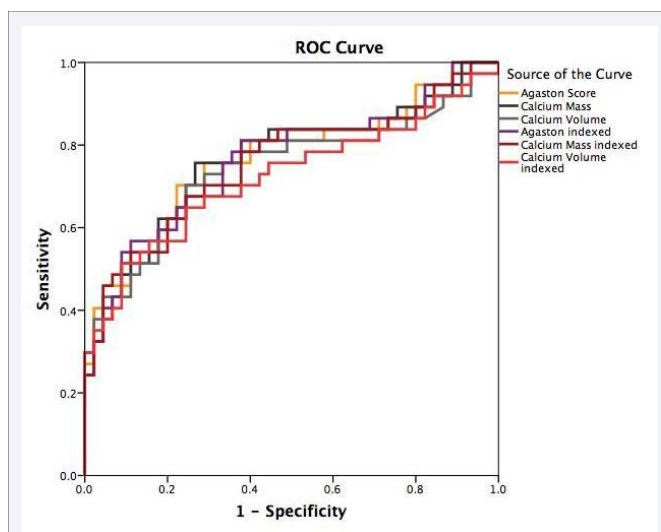


Figure 1 Receiver operating characteristic (ROC) curve comparing Agatston score with Calcium mass score and Calcium volume score. Curve also demonstrates and compares the indexed valve calcium scores which were obtained after adjusting the scores for valve areas.

Table 2: ROC curve statistics.

Test	C Statistics
Agatston Score	0.768
Calcium Mass	0.764
Calcium Volume	0.741
Agatston indexed	0.767
Calcium mass indexed	0.723
Calcium volume indexed	0.723

Table 3: ROC cutoff scores.

AVC Calcium cutoff	Sensitivity (%)	Specificity (%)	1-Specificity (%)
631	81%	40%	60%
785*	76%	71%	29%
1651**	47.4%	89.1%	10.9%
1850	47.4%	95.7%	4.3%

*Optimum value for both sensitivity and specificity (Youden's J statistic) (22) **Value previously reported (14)

C-statistic of .887. Considering that a C-statistic between 0.9 to 1 is considered an "excellent" test, 0.80 to 0.90 is considered a "good" test, and 0.70 to 0.80 is considered a "fair" test, our results suggest the various calcium scoring methods fall within a range of "good", yet approaching the level of "excellent" for classifying patients correctly with severe aortic stenosis.

Interestingly, we observed mean differences in these C-statistics, whereby the Agatston scoring method demonstrated the largest area under the curve. Follow-up comparisons of the C-statistics revealed the calcium scoring systems did not statistically differ in their ability to classify patients, suggesting Agatston system is as valid of a test as calcium mass and calcium volume scoring systems. The analysis was repeated with indexing for sinotubular junction size, body mass index and body surface area and there was no improvement in the predictive model. ROC curve analyses were conducted again after excluding patients with a bicuspid valve or atrial fibrillation, yet the results remained unchanged.

The mean aortic valve calcium (AVC) score obtained by Agatston scoring method was 1513 Agatston units (AU) (range - 35.4 - 7267 AU). The inter observer AVC score variability was <3%. The Youden's J statistic, the optimum value for both sensitivity and specificity for predicting severe aortic valve stenosis by echocardiography, was provided by a score of 785 AU (Sensitivity = 76%, Specificity = 71%; [16]. A score of 1651 AU (used by other investigators) had a specificity of 89% for characterizing patients with severe aortic stenosis (iAVA <0.6 cm²/m²) and a score of 1850 had a specificity of 96% for characterizing patients with severe aortic Stenosis [14].

In the subset of low-flow - low- gradient (LF-LG) aortic stenosis patients in our study, a score of 1850 AU captured 20/22 patients with low gradient, severe AS (Figure 2).

DISCUSSION

This is the first study to systematically assess various approaches to aortic valve calcium scoring as an adjunct to

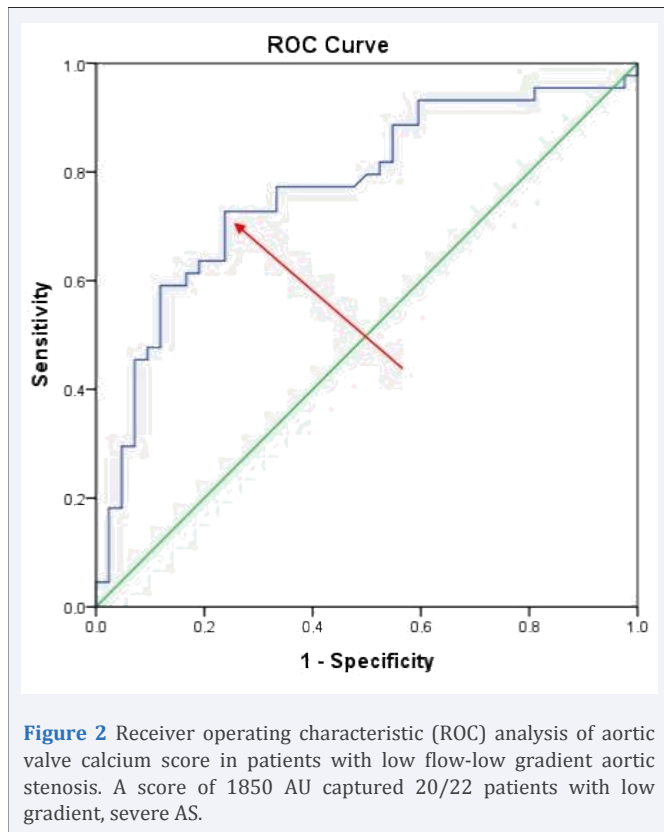


Figure 2 Receiver operating characteristic (ROC) analysis of aortic valve calcium score in patients with low flow-low gradient aortic stenosis. A score of 1850 AU captured 20/22 patients with low gradient, severe AS.

diagnostic echocardiography for aortic valve stenosis. We observed a good correlation between the degree of aortic valve calcium assessed on multidetector CT and hemodynamic severity measured using TTE in this series of patients with aortic stenosis.

While other authors have suggested calcium volume and calcium mass score scoring for AVC, in our study the use of straightforward Agatston method of scoring without indexing appears to be at least as good as the other approaches [14]. We did not observe improvement in the predictive model after indexing for aortic valve size or body size.

Prior studies have shown that the echocardiographic agreement and optimal cut points of aortic valve calcium scores are different in women than men, perhaps related to the size of the aortic valve - the same amount of calcium in a small aortic valve should cause more obstruction than in a large aortic valve [17]. AVA would thus be smaller in individuals with a small body size and/or a small aortic annulus size. We thus attempted to index for aortic size (using CT sinotubular junction diameter as a surrogate for aortic annulus size) and body size, but these indexes did not improve upon the predictive model.

While Doppler echocardiography remains the mainstay for assessing the severity of aortic stenosis, there are well known limitations such as inability of Doppler echocardiography to provide direct pressure measurement, the need for LVOT measurements, and the need for adequate imaging windows for careful measurements to assure accuracy [7,8]. Also, in patients with depressed EF and low-flow low-gradient, Doppler echocardiography may not accurately assess the AS severity [8,18].

In clinical practice, the subsets of patients with LF-LG severe aortic stenosis are sometimes challenging to diagnose. Some patients with symptomatic aortic stenosis, but low gradients do not receive surgery and have a high mortality. [18-22]. Transcatheter aortic valve implantation (TAVI) has become a new standard of care for patients with aortic stenosis who are not suitable candidates for surgery [23]. In patients with low flow low gradient aortic stenosis, TAVI has a potential to improve survival [24]. However, the frequency of paradoxical low gradient severe aortic stenosis is debated and the evaluation and management of these patients remains controversial [21,22]. Our study had a relatively large fraction of patients with low gradient severe AS. The finding that 20/22 (90%) of patients with an aortic valve calcium score >1850 were correctly categorized as having severe aortic stenosis leads us to suggest that these aortic valve calcium scores could be useful tools to help establish this sometimes challenging diagnosis.

Our findings have significant clinical implications, measurement of the degree of aortic valve calcification on MDCT can serve as an accurate and complimentary method to TTE and dobutamine stress echocardiography for the assessment of the severity of AS. One important clinical use of calculating aortic valve calcium score would be in patients who are critically ill with heart failure and aortic stenosis and are being considered for surgical aortic valve replacement or TAVR. Benefits of such aggressive therapies are often not clear as frequently these patients presents with low gradient. Presence of significant calcification as measured by the AVA calcium score, might provide confirmation of severe aortic stenosis and would assist in clinical decision-making in aortic valve replacement.

Other authors have demonstrated the usefulness of aortic valve calcium score calculated by quantitative CT in evaluation of severe aortic stenosis in the setting of low gradient [25]. For example, Askoy and colleagues found that the patients in the category of severe AS with low LVEF who had more heavily calcified valves had worse prognosis.

In our analysis, we did not find a difference in the performance calcium scoring when patients with bicuspid aortic valve were excluded. Ren and colleagues recently reported the results of their study of aortic valve calcification in patients with bicuspid aortic valve disease and showed results similar to our study [26]. Major Limitations of our study include its retrospective design and the fact that it is single center with a somewhat modes sample size. Also, AVC by MDCT and Doppler echocardiography did not take place simultaneously and clinical outcomes were not examined for this study. Information on number patients and results of invasive measurement and dobutamine stress echo for assessment of severity of Aortic stenosis was not available for our analysis.

A different statistical approach such as square root transformation normalization would have been preferable, but was not feasible given the number of subjects and the statistics employed might be considered descriptive. However, despite these limitations, the results do offer further evidence that MDCT aortic valve calcium scoring has usefulness in the diagnosis of aortic valve stenosis.

CONCLUSION

Aortic valve calcium assessed on MDCT correlates reasonably well with the severity of aortic stenosis by echocardiography. The use of the straight forward Agatston method for scoring without indexing appears to be the optimal approach. Aortic valve calcium scoring may be a helpful modality for diagnosing the subgroup of patients with low gradient, severe aortic stenosis.

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