A Novel Two-Dimensional Echocardiography Method to Objectively Quantify Aortic Valve Calcium and Predict Aortic Stenosis Severity

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Aortic valve calcium (AVC) is a strong predictor of aortic stenosis (AS) severity and is typically calculated by multidetector computed tomography (MDCT). We propose a novel method using pixel density quantification software to objectively quantify AVC by two-dimensional (2D) transthoracic echocardiography (TTE) and distinguish severe from non-severe AS. A total of 90 patients (mean age 76 ± 10 years, 75% male, mean AV gradient 32 ± 11 mmHg, peak AV velocity 3.6 ± 0.6 m/s, AV area (AVA) 1.0 ± 0.3 cm^2, dimensionless index (DI) 0.27 ± 0.08) with suspected severe aortic stenosis undergoing 2D echocardiography were retrospectively evaluated. Parasternal short axis aortic valve views were used to calculate a gain-independent ratio between the average pixel density of the entire aortic valve in short axis at end diastole and the average pixel density of the aortic annulus in short axis (2D-AVC ratio). The 2D-AVC ratio was compared to echocardiographic hemodynamic parameters associated with AS, MDCT AVC quantification, and expert reader interpretation of AS severity based on echocardiographic AVC interpretation. The 2D-AVC ratio exhibited strong correlations with mean AV gradient ($r = 0.72$, $p < 0.001$), peak AV velocity ($r = 0.74$, $p < 0.001$), AVC quantified by MDCT ($r = 0.71$, $p < 0.001$) and excellent accuracy in distinguishing severe from non-severe AS (area under the curve = 0.93). Conversely, expert reader interpretation of AS severity based on echocardiographic AVC was not significantly related to AV mean gradient ($t = 0.23$, $p = 0.64$), AVA ($t = 2.94$, $p = 0.11$), peak velocity ($t = 0.59$, $p = 0.46$), or DI ($t = 0.02$, $p = 0.89$). In conclusion, these data suggest that the 2D-AVC ratio may be a complementary method for AS severity adjudication that is readily quantifiable at time of TTE. Published by Elsevier Inc. (Am J Cardiol 2021;156:108−113)

Aortic valve stenosis (AS) is a degenerative inflammatory process driven largely by fibrosis and changes in calcium homeostasis leading to aortic valve (AV) calcium, thickening, and outflow obstruction.[1,2] Stenosis severity is most commonly adjudicated via echocardiography using the peak aortic jet tract obstruction velocity, mean pressure gradient, aortic valve area (AVA), and dimensionless index (DI).[3] Aortic valve calcium (AVC) is also utilized to adjudicate AS severity, and it is most commonly quantified by multidetector computed tomography (MDCT).[4-8] Analogous transthoracic echocardiography (TTE) methods have been proposed previously to allow for real time AVC data similar to what MDCT provides.[9] However, this method relies on three-dimensional (3D) echocardiographic techniques which may require additional training to incorporate into practice. We propose a simple, novel two-dimensional (2D) TTE method for AVC quantification using a publicly available pixel density software. This study compares AVC quantification using pixel density with MDCT calcium quantification and echocardiographic hemodynamic criteria for AS, and examines this method's ability to distinguish severe from non-severe AS.

Methods

Patients with suspected severe aortic stenosis undergoing 2D echocardiography for work up were retrospectively evaluated at the University of Illinois at Chicago and the Jesse Brown Veteran Affairs Hospital in Chicago, IL between 2017 and 2020. This study was approved by the institutional review board. Of the 100 patients initially evaluated for inclusion, 90 had adequate short axis TTE images for analysis. Ten patients were excluded due to excessive acoustic shadowing on short axis TTE images of the AV that precluded accurate AV pixel density analysis and AVC quantification.

Echocardiography studies were performed at our institution by trained sonographers using a commercially available echocardiography system. A standardized, comprehensive imaging protocol that included detailed assessments of valvular and ventricular function was employed according to American Society of Echocardiography guidelines.

Typical echocardiographic hemodynamic indicators of AS were retrospectively measured by a single user familiar

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with echocardiographic image interpretation to decrease reader to reader variability. To meet inclusion criteria, patients were required to have echocardiographic evidence of severe AS which was defined as at least one of the following: mean transvalvular gradient ≥40 mmHg, peak transvalvular velocity ≥ 4 m/s, AVA ≤ 1 cm^2, DI ≤ 0.25, or suspected severe AS with likely low flow states or poor Doppler windows. Only patients with a majority of the annulus visible on short axis images were included to allow for an adequate gain baseline and those with acoustic shadowing limiting annulus visualization were excluded. A ratio between the average pixel density of the AV and that of the aortic annulus itself was calculated to produce a gain and gray-scale independent ratio (2D-AVC ratio, Figure 1).

Two expert readers independently analyzed the 2D short axis AV TTE images to assess for the presence of severe or non-severe AS based on a qualitative interpretation of AVC severity by TTE. The expert readers were blinded to MDCT calcium score and TTE hemodynamic data.

Brightness or luminance of the light emitted by an LCD display corresponding to AVC was measured using the free, publicly available pixel density quantification software, ImageJ (developed by the National Institute of Health- http://imagej.nih.gov./ij/docs/guide). Single parasternal short axis still frames of the AV in end-diastole in which the entire aortic annulus and leaflet tips were visible were chosen for each patient and analyzed using ImageJ. The average pixel density of the short axis AV was measured and recorded as the mean grayscale value, with 0 representing a black pixel and 255 representing a white pixel. The AV was defined as the entire area contained within the roughly triangular geometric shape that resulted from tracing the aortic annulus in short axis with the "polygon" tool in ImageJ. The average pixel density of the aortic annulus itself was similarly measured using the "segmented line" tool in ImageJ. The "segmented line" tool measures the average pixel density only within the line itself that was traced around the aortic annulus (as opposed to the area of the entire roughly triangular shape obtained with the "polygon" tool).

Electrocardiographically-gated contrast enhanced MDCT (Revolution Evo CT 750HG; GE Healthcare, Chicago, IL) was used to quantify MDCT AV calcium score. A standardized acquisition protocol was used, acquiring 64 contiguous transverse slices (thickness 2.5 mm, 120 keV, 5 mAs, rotation time 0.35 s, field of view = 25 cm). AVC measurements were performed offline on a dedicated workstation (Osirix version 12.0.0). All contrast enhanced computed tomography scans were performed within 3 months of TTE imaging for consideration of TAVR. MDCT calcium score is most typically obtained with non-contrast CT imaging, however alternative methods for contrast CT imaging have been published which we utilized in this study as only contrast enhanced imaging was available in our population.[10] To subtract the contrast enhancement, a region of interest was obtained in the ascending aorta excluding valvular calcium to determine the mean Hounsfield Unit (HU) value of the contrast enhancement. A calcified AV lesion was defined as more than three contiguous pixels with a peak of attenuation of the mean HU + 100 HU. MDCT calcium score was calculated by using the Agatston (AU) method, by adding up the score on each slice of the MDCT AV image. Extravalvular calcium (e.g., from the mitral valve annulus, the ascending aorta, and coronary arteries) was excluded.

Statistical analysis was performed using IBM SPSS (version 26, Armonk, New York) and R (version 4.0.3, Vienna, Austria). Data are presented as mean ± SD or as percentages. 2D-AVC ratio and MDCT scores were compared with echocardiographic hemodynamic parameters using simple linear regression. Area under the receiver operating characteristic curve was used to determine the accuracy of 2D-AVC ratio for identifying severe AS. Expert reader analysis was compared using Cohen's Kappa statistic. Intraclass correlation was used to evaluate reproducibility of 2D-AVC ratio measurements and MDCT calcium scoring. P values < 0.05 were considered statistically significant.

Results

A total of 90 of the 100 screened patients with suspected severe aortic stenosis undergoing 2D echocardiography for work up met inclusion criteria and were retrospectively evaluated (10 patients excluded due to poor short axis images not amenable to 2D-AVC ratio quantification). Baseline demographic, echocardiographic, and MDCT characteristics are summarized in Tables 1 and 2. MDCT calcium score averages were based on the 47 patients with CT angiography available for CT calcium score quantification. The 2D-AVC ratio exhibited excellent correlation

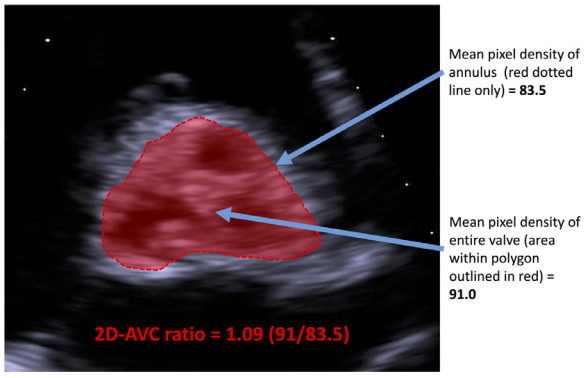


Figure 1. The 2D-AVC ratio. 2D-AVC = two-dimensional aortic valve calcium.

Table 1
Baseline clinical and demographic data for suspected severe aortic stenosis population.

Baseline Characteristic	Patients with multi-detector computed tomography data n = 47	Overall population n = 90
Age, years	77 ± 9	76 ± 10
Male	41 (87.2%)	76 (84.4%)
Race		
White	28 (59.6%)	48 (53.3%)
African American	15 (31.9%)	28 (31.1%)
Hypertension	42 (89.2%)	83 (92.2%)
Hyperlipidemia	40 (85.1%)	73 (81.1%)
Diabetes mellitus	15 (31.9%)	33 (36.7%)
Coronary artery disease	35 (74.5%)	62 (60.8%)

Table 2
Baseline transthoracic echocardiographic and multidetector computed tomography data for suspected severe aortic stenosis population.

Baseline imaging data	Patients with multi-detector computed tomography data n = 47	Overall population n = 90
Aortic valve calcification ratio, overall	0.86 ± 0.24	0.88 ± 0.21
Male (n = 76)	0.85 ± 0.23	0.88 ± 0.22
Female (n = 14)	0.95 ± 0.25	0.94 ± 0.20
Multidetector computed tomography, Agatston units, overall	6818 ± 4059	
Male (n = 41)	6720 ± 4065	
Female (n = 6)	7482 ± 4337	
Aortic valve mean gradient, mmHg	31 ± 12	32 ± 11
Aortic valve maximum velocity, m/s	3.6 ± 0.7	3.6 ± 0.6
Aortic valve area, cm^2	1.0 ± 0.3	1.0 ± 0.3
Dimensionless index	0.26 ± 0.06	0.27 ± 0.08
Ejection fraction (%)		
50-70%	37 (82.2%)	71 (81.6%)
40-49%	1 (2.2%)	3 (3.4%)
30-39%	3 (6.7%)	6 (6.9%)
<30%	4 (8.9%)	7 (8.0%)
Aortic stenosis severity		
Mild	0 (0%)	1 (1.1%)
Moderate	16 (34.0%)	32 (36.8%)
Severe	30 (63.8%)	54 (62.1%)

with AVC quantified by MDCT (r = 0.71, p <0.001, Figure 2) and excellent accuracy in distinguishing severe from non-severe AS (area under the curve = 0.93, Figure 3). The ideal cutoff value for 2D-AVC ratio to distinguish severe from non-severe AS was 0.96 (89% specificity, 89% sensitivity, Figure 3) for the overall population. Similar cutoffs were found when stratified by sex (0.95 cutoff, 83% sensitivity, 86% specificity for females; 0.97 cut off, 90% sensitivity, 87% specificity for males). AVC quantification by 2D- AVC ratio and MDCT correlated well with multiple echocardiographic hemodynamic parameters including mean gradient (r = 0.72, p < 0.001 for 2D-AVC ratio and r = 0.66, p <0.001 for MDCT, Figure 4) and peak velocity (r = 0.74, p < 0.001 for 2D-AVC ratio and r = 0.68, p <0.001 for MDCT, Figure 4). There were less robust correlations with AVA (r = -0.23, p = 0.03 for 2D-AVC ratio and r = -0.12, p = 0.4 for MDCT) and dimensionless index (r = -0.23, r = 0.04 for 2D-AVC ratio and r = -0.20, p = 0.2 for MDCT). Univariate and multivariate regressions yielded no significant relationships with demographic and baseline risk factor variables (age, sex, race, hyperlipidemia, diabetes mellitus, or coronary artery disease) and the 2D-AVC ratio (r = 0.22, p = 0.64).

Expert reader analysis of AS severity based solely on qualitative TTE AVC assessment was also evaluated and compared to echocardiographic parameters associated with AS. Our expert reader assessment was not significantly related to AV mean gradient (t = 0.23, p = 0.64), AVA (t = 2.94, p = 0.11), peak velocity (t = 0.59, p = 0.46) and DI (t = 0.02, p = 0.89). Similarly, we compared two independent expert reader analyses of AS severity based on qualitative AVC TTE assessment which revealed significant disagreement (Kappa = 0.12). Additionally, expert reader analysis was not significantly related to 2D-AVC ratio (t = 1.12, p = 0.31).

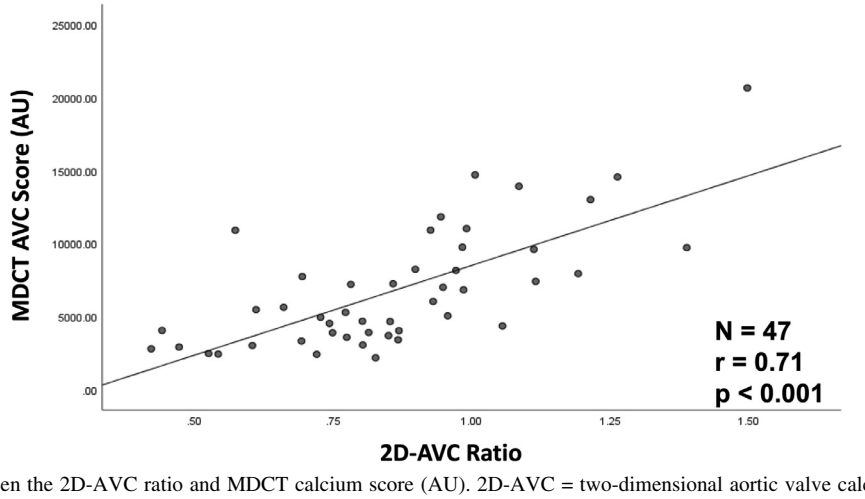
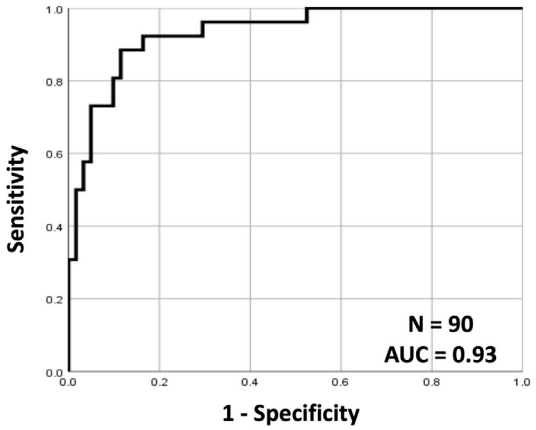


Figure 2. Correlation between the 2D-AVC ratio and MDCT calcium score (AU). 2D-AVC = two-dimensional aortic valve calcium; AU = Agatston unit; MDCT = multidetector computed tomography.



Threshold	Specificity	Sensitivity
0.94	0.82	0.92
0.96	0.89	0.89
0.99	0.90	0.77

Figure 3. Receiver operator curve to assess the diagnostic accuracy of the 2D-AVC ratio in differentiating severe from non-severe AS with an ideal cutoff of 0.96 (sensitivity 89%, specificity 89%). 2D-AVC = two-dimensional aortic valve calcium; AS = aortic stenosis.

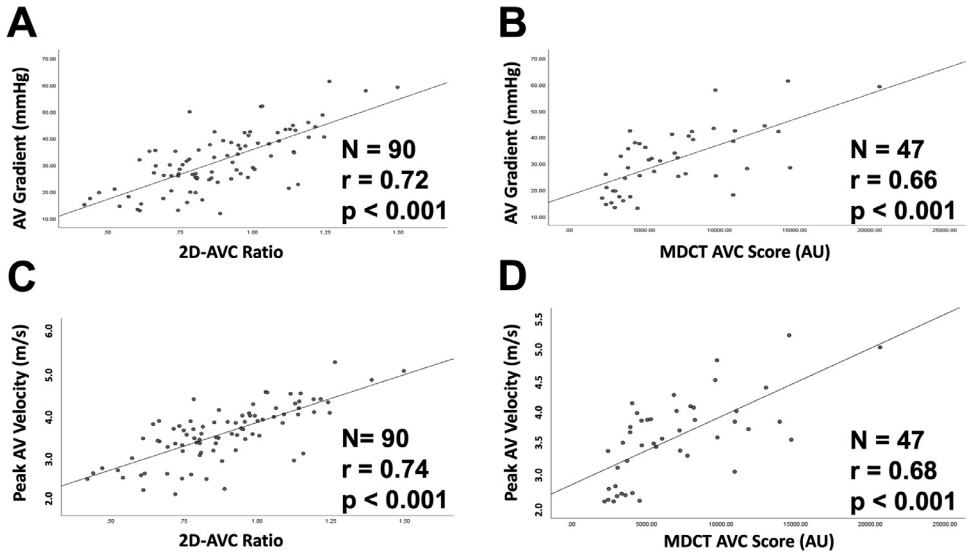


Figure 4. **(A)** Correlation between 2D-AVC ratio and mean AV gradient (mmHg), **(B)** MDCT calcium score (AU) and mean AV gradient (mmHg) **(C)** 2D-AVC ratio and peak AV velocity (m/s), and **(D)** between MDCT calcium score (AU) and peak AV velocity (m/s). 2D-AVC = two-dimensional aortic valve calcium; AU = Agatston unit; AV = aortic valve; MDCT = multidetector computed tomography.

Intraclass correlation (ICC) was used to evaluate reproducibility of 2D-AVC ratio measurements in 10 random patients and demonstrated excellent reproducibility (ICC = 0.95, p <0.001 for intra-rater reliability and ICC = 0.71, p = 0.04 for inter-rater reliability).

Discussion

Our study revealed that the described 2D-AVC ratio correlates with MDCT calcium score and echocardiographic hemodynamic measures of AS. Consequently, the 2D-AVC ratio may provide a simple, gain-independent, quantitative bedside assessment of AVC that predicts AS severity. AVC as measured by both echocardiography and MDCT has previously been shown to predict progression of outcomes in patients with AS including death, need for AV replacement, and prosthetic valve regurgitation.[6,11] In terms of AVC quantification, TTE and more recently MDCT have been utilized. TTE techniques have ranged from visual estimation of AVC to more sophisticated techniques such as integrated backscatter and 3D echocardiography calcium scoring.[9,11,12] The more sophisticated methods such as integrated backscatter and 3D echocardiographic reconstruction require complex offline image analysis.[9,12] These factors have limited these echocardiographic quantification modalities from becoming routine measurements.[9,11,12]

In contrast to the limitations noted with echocardiography, AVC quantification by MDCT allows for 3D visualization of the calcium contained within the AV and accurately discriminates AV from non-AV calcium. These previous MDCT studies were validated with non-contrast CT studies given the increased difficulty in distinguishing calcium from intravenous contrast by CT.[6,13] Despite this difficulty, recent studies have established methods for determining AVC quantification with contrast CT angiography which have been shown to correlate with non-contrast MDCT AVC quantification.[10,14] We employed AVC quantification from our patients' contrast pre-TAVR CT angiography to compare to the 2D-AVC ratio which did not include non-contrast studies. Although CT angiography based AVC

scores have been shown to correlate with non-contrast quantification, we must emphasize that CT angiography is not the recommended method for AVC quantification which is why we did not use this as a gold standard for AS severity in our study. The Agatston scores calculated in our study are generally higher than non-contrast studies (due to the contrast elevating the baseline Hounsfield units) and must be interpreted with caution.

The 2D-AVC ratio exhibited a strong correlation with hemodynamic echocardiographic markers of AS and AVC as measured by MDCT calcium score. Pixel density as measured from ultrasound images of plated calcium has been shown to strongly correlate to both calcium weight and CT calcium score which is why this measurement was chosen to derive the 2D-AVC ratio.[15] Pixel density quantification has also previously been utilized in echocardiographic studies of aortic stenosis by measuring echocardiographic Doppler signals.[16] Although previous echocardiographic techniques have been developed to quantify AVC, they require offline 3D image analysis and the authors do not supply a precise methodology for replicating their AVC quantification[9,12] This is not the case for our method which involves only two measurements from the short axis view of the aortic valve that we have given detailed instructions for obtaining previously in this article. Additionally, methods previously published regarding 3D echocardiographic AVC quantification require preset gains. This is in contrast to the 2D-AVC ratio which is gain independent. Furthermore, the 2D-AVC ratio outperforms expert reader analysis of AS severity based on echocardiographic AVC assessment.

Although the 2D-AVC ratio exhibited strong correlations with echocardiographic measures of severe AS (mean gradient and peak velocity) and AVC as measured by MDCT, there were less robust with AVA and DI. We suspect the less robust correlation is due to the increased number of measurements needed to obtain AVA by the continuity equation and DI as opposed to single measurements need to mean gradient and peak velocity which may lead to more variability in measurements. Additionally, no significant relationship was found between demographic and clinical characteristics (age, race, sex, presence of cardiovascular comorbidities) and the 2D-AVC ratio. In contrast to MDCT which shows a clear distinction in calcium score cut-offs for severe AS for males and females, we found a very similar 2D-AVC ratio cut off for males and females in our study. We suspect a larger cohort of patients is necessary to fully delineate these demographic relationships with the 2D-AVC ratio.

This study was limited by its retrospective nature and relatively small sample size (although this sample size is comparable to previous studies evaluating echocardiographic quantification of AVC). The 2D-AVC ratio also relies on excellent short axis AV echocardiographic images with a clearly delineated annulus to serve as an echocardiographic gain baseline which may be difficult to obtain in some patients due to body habitus. Additionally, this method needs to be evaluated in larger cohorts of patients utilizing multiple echocardiographic systems. The present study did not address clinical scenarios such as low-flow, low-gradient AS but may be further explored in future studies similar to what has already been shown with MDCT.[17] Additionally, acoustic shadowing limited us from performing a cusp by cusp echocardiographic calcium quantification, which has been shown to be additive in the MDCT literature.[18] Finally, this method needs to be validated in a wider spectrum of AS severity given the smaller number of non-severe AS patients in this study (38%) to better characterize the sensitivity and specificity of detecting severe AS with the 2D-AVC ratio.

In conclusion, the 2D-AVC ratio exhibits excellent correlations with MDCT calcium score, outperforms expert reader echocardiographic AVC interpretation, and can discriminate severe from non-severe AS. Our study suggests that the 2D-AVC ratio may be a complementary method for AS severity adjudication that is readily quantifiable at time of TTE.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosures

None

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