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Quantitative analysis of spectral Doppler clicks in assessment of aortic stenosis

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Abstract

Objectives: This study was performed to evaluate an additional echocardiographic spectral Doppler marker, which would identify severe aortic stenosis (AS).

Background: Echocardiography is most commonly utilized to assess AS and has been validated against invasive measurements. However, the data obtained are not always in agreement, leaving a conundrum regarding the true severity of AS and can lead to other diagnostic procedures. This highlights the importance of improved noninvasive diagnostic techniques.

Methods: Forty-eight indeterminate cases of calcific AS that had been previously evaluated by both echocardiography and cardiac catheterization were included in the study, using cardiac catheterization as the gold standard for calculation of aortic valve area (AVA). The intensity of opening and closing of the aortic valve, represented by bright vertical deflections on the CW spectral waveform, was quantified using ImageJ software to generate pixel intensity histograms to create opening and closing click (OC and CC) ratios. These ratios were compared with echocardiographic variables and catheterization AVA.

Results: Thirty-five patients were found to have severe AS and 13 patients were found to have nonsevere AS, as assessed by cardiac catheterization. CC ratio was found to be a significant predictor of severe AS with an OR 0.024 (95% CI: 0.002-0.378, P = .0079). Adding CC to a model using standard echocardiographic parameters resulted in significant improvement in the C-statistic (0.693 to 0.835, P = .0134).

Conclusions: An additional Doppler marker measuring the aortic valve CC ratio has been found to improve detection of severe AS.

KEYWORDS

aortic stenosis, aortic valve closing click, aortic valve opening click, cardiac catheterization, echocardiography, pixel density histogram, spectral doppler

1 | INTRODUCTION

Aortic stenosis (AS) is known to cause significant morbidity including heart failure, chest pain, and syncope. Patients with severe symptomatic AS have a known poor prognosis. The prevalence of AS increases with age and is one of the most common valvular lesions among the elderly.[1,2]

AS is commonly caused by degenerative calcification of the valve. These changes occur due to inflammation and deposition of lipids and calcium nodules. As calcification progresses, the leaflet mobility becomes progressively reduced which results in obstruction to left

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ventricular outflow.[1,3-5] This can occur with a normal trileaflet valve or a congenitally abnormal aortic valve, most commonly a bicuspid valve. Another common cause of AS globally is rheumatic valvular disease. However, in North America, AS is primarily due to calcific disease.[2]

AS is typically suspected first based on history and physical examination. Cardiac auscultation detects valve sounds which are transmitted vibrations or pressure waves that are believed to be the result of rapid acceleration or deceleration of blood.[6] A common physical examination finding of AS is a crescendo/decrescendo systolic ejection murmur. As AS progresses the duration of the murmur increases, the peak of this murmur is heard later in systole, closer to the aortic closure sound (A2). With more advanced AS, there may be a reduced or absent aortic closure sound (A2).[2] A delayed slow rising carotid upstroke is also often appreciated with more severe stenosis given increased flow obstruction but this finding is less prominent in the elderly.[3,5]

Echocardiography is the standard imaging modality utilized to assess the severity of aortic stenosis. 2D imaging and Doppler are used to assess mean transvalvular gradient, maximum aortic jet velocity (Vmax), dimensionless index (DI), and aortic valve orifice area (AVA) as calculated from the continuity equation. Echocardiography has been validated in comparison with invasive measurements.[3] However, the combination of the data obtained utilizing echo methods is not always in agreement, leaving a conundrum regarding the true severity of AS and can lead to transesophageal echocardiography, CT, MRI, or an invasive procedure such as cardiac catheterization.[7-12] This highlights the importance of improved noninvasive diagnostic techniques. It is clearly valuable to correctly identify the severity of AS to ensure patients receive the appropriate clinical management.

1.1 | OBJECTIVES

It is clear that finding an additional echocardiographic feature to help identify a severely stenotic aortic valve would be valuable. We have observed that in the continuous-wave (CW) Doppler of normal valves, the opening and closing of the aortic valve is accompanied by a bright vertical deflection from the baseline at the beginning and end of systole. Comparable to the audible component of A2 diminishing or absent on auscultation of severe AS, the ultrasonic manifestation of this same event should be similar on echo. We hypothesized that in severe calcific AS, the opening and closing bright vertical deflections (clicks) would be diminished or absent due to the restricted mobility of the valve leaflets. This was shown in a subjective study which was blinded to echo velocity and gradient results and clicks were described as being present or absent as shown in Figure 1.[13] Subsequently, we have developed a technique to objectively quantify the intensity of the opening click (OC) and closing click (CC), which could assist in the assessment of AS.

2 | METHODS

In this study, we used the same group of patients as the original blinded study which was a retrospective chart review of all cases of calcific AS in adults that were evaluated by both cardiac catheterization and echocardiography performed within twelve months of each other at the University of Illinois Hospital between January 1, 2006, and July 1, 2012. The study was approved by the Institutional Review Board Committee on Human Research. The study included adult patients over the age of 18 with suspected calcific AS. Congenital AS including bicuspid aortic valves was included. Patients with prior aortic valve repair or replacement were excluded. The final number of patients included in the study was 48.

2.1 | Cardiac catheterization

Cardiac catheterization was used as the gold standard for the true aortic valve orifice area for this study, and the calculated aortic valve area (AVA) was indexed for body surface area (BSA). The AVAs were calculated using the Gorlin Equation via cardiac outputs obtained by thermodilution or the Fick method. If thermodilution was not performed, then the AVA was calculated using an assumed oxygen consumption (Fick-based) equation. Transvalvular gradient was determined by catheter pullback across the aortic valve or the use of a double lumen catheter.

2.2 | Routine echo analysis

Patients' echo data in closest proximity to the catheterization (maximum time differential of 12 months) were reviewed. Transthoracic echocardiograms were obtained with Siemens 512 echo machines, using standard CW Doppler gain settings for evaluation of the left ventricular outflow tract in the apical views. A Pedoff probe for evaluation of the aortic valve velocities was also used. Each patient's Vmax (m/s), mean aortic valve gradient (mm Hg), dimensionless index DI (LVOT VTI/aorta VTI), and calculated AVA (cm^2) using the continuity equation indexed for BSA was collected. Left ventricular ejection fraction was determined using the Simpson's biplane method. The ACC/AHA guidelines for the values that define severe aortic stenosis were used in this study.[14]

2.3 | CW spectral Doppler Analysis with the ImageJ histogram

The spectral Doppler recording consists of a series of bins (vertical axis) that are recorded over time (horizontal axis). At any given point in time there a differential speed of movement of red cells with more red cells moving at the velocity of the most intense bin than are moving at other velocities which are less intense bins. The intensity of any bin refers to brightness. The aortic valve opening click (OC) and closing click (CC) represent rapid acceleration and deceleration of red cells.

Brightness or luminance of the level of light emitted by an LCD display of the spectral Doppler waveform was measured using

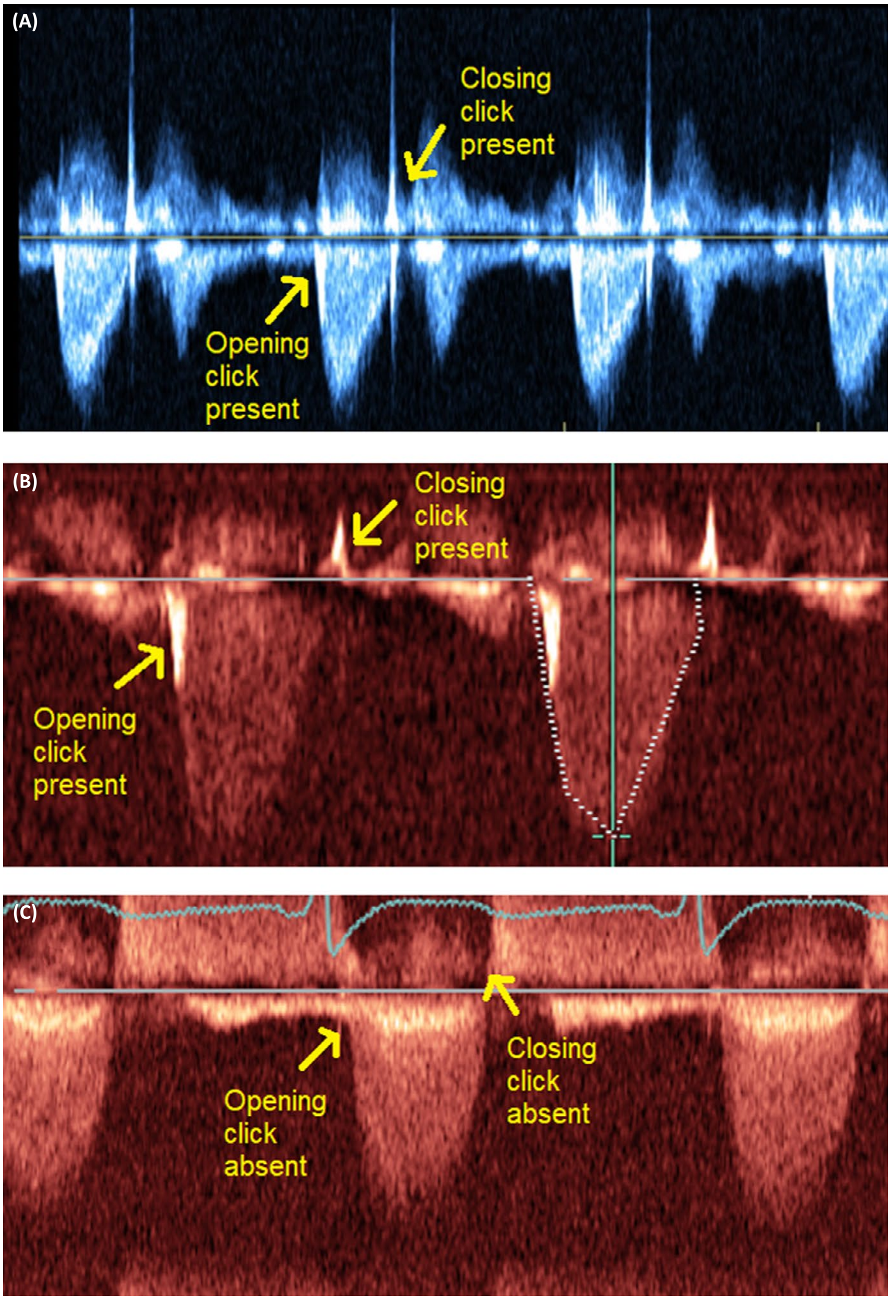

FIGURE 1 Continuous-wave Doppler of three different patients' aortic valves. (A) Healthy patient demonstrating the presence of an opening click and closing click. (B) Patient with suspected severe aortic stenosis but demonstrating the presence of an opening click and a closing click. (C) Patient with severe aortic stenosis but demonstrating the absence of both opening and closing clicks

ImageJ software (developed by the National Institute of Health-http://imagej.nih.gov./ij/docs/guide). Using this offline technology, pixel intensity histograms were created.

For this study, Doppler gray scale and gain were set to allow signals that were adequate in appearance revealing laminar flow without excessive background noise. Because a number of variables determine spectral waveform brightness, click pixel intensity was normalized to the baseline peak pixel intensity of the spectral Doppler waveform creating click baseline ratios. Measurements were made independently by 3 residents familiar with Doppler technology and ImageJ software. For the OC, a region of interest was drawn around the CW Doppler waveform starting at the QRS complex including the bright portion of the spectral Doppler waveform (1 m/s) and extended to the end of ejection. We determined that by analyzing normal click patterns in healthy patients that the opening click invariably occurred within this region of interest. The selected region of interest was then analyzed using the ImageJ "plot profile" function under the "Analyze" drop box. A histogram was generated with "Gray Value" on the y-axis and "Distance" in pixels on the x-axis. Using the "List" button in the bottom left of the histogram, a numerical table of "Plot Values" was displayed which corresponded to the varying mean pixel intensities along different points of the CW Doppler waveform. The pixel intensity of OC was divided by the baseline peak pixel intensity of the spectral Doppler waveform creating an OC/peak baseline ratio or relative intensity ratio.

For the CC histogram, a region of interest was drawn around the CW Doppler waveform starting at the last 25% of aortic ejection period and extended thru the ejection period. CC pixel intensity was evaluated by its intensity at 1 m/s above the baseline. The pixel intensity of the CC was divided by the baseline peak pixel intensity of the spectral Doppler waveform obtained from the OC histogram creating a CC/peak baseline ratio or relative intensity ratio (Figures 2 and 3).

2.4 | Statistical analysis

Categorical variables were summarized as counts and percentages, and continuous variables were summarized as mean ± standard deviation (*SD*). Bivariate analyses of a continuous and categorical variable were assessed using two sample t test or Wilcoxon rank-sum test (Mann–Whitney U test) as appropriate, and two categorical variables were assessed using the Chi-square test for independence or Fisher's exact test as appropriate. Multivariate analysis was performed with logistic regression. Due to small sample size, variable selection methods such as backward elimination and stepwise were used to select the important variables. Two sample t test, simple logistic regression, and sensitivity analysis were performed to determine the severe aortic stenosis using the CC cutoff (threshold) value for the dichotomization. Statistical software SAS 9.4 was used to conduct the entire statistical analysis.

3 | RESULTS

3.1 | Interobserver variability

OC and CC ratios of 28 patients were measured by exactly one resident, and the remaining twenty patients were measured by two (at least two) residents. Among those patients whose CC ratio was observed by two residents, the interobserver reliability measured by the intraclass correlation, which is the Pearson correlation coefficient between two observers' measurements, was 0.97. Among those patients whose OC ratio was measured by the two residents, the interobserver reliability measured by the intraclass correlation was 0.94. These large positive correlations indicate high degree of interobserver reliability and that the physicians' measurements are interchangeable.

Echocardiographic variables and click ratios as compared to catheterization presence or absence of severe aortic stenosis:

Standard echocardiographic measures were used for the presence of severe aortic valve stenosis:

Maximum velocity (V_{max}) of 4 m/s or greater

Mean gradient 40 mmHg or greater

DI of 0.25 or less

AVA by continuity equation 1 cm^2 or less

These echocardiographic measures for severe AS were compared with the cardiac catheterization AVA with the standard of 1 cm^2 or less as indicative of severe aortic valve stenosis (Table 1).

A total of 48 subjects were included in this study. Table 1 shows that 35 patients had severe AS and 13 patients did not have severe AS as validated by cardiac catheterization. Age, gender, and left ventricular ejection fraction showed no significant difference when compared to the presence or absence of cardiac catheterization proven severe AS (Table 1). Several echocardiographic measures including BSA, Vmax, DI, and AVA cm^2 were also found to be statistically significant. Of all these measures, notably the mean difference in AVA cm^2 with an OR 5.40 (95% CI: 1.38-21.20) was the most statistically significant measure. Mean values ± standard deviation were also shown for OC ratios and CC ratios for patients with and without severe aortic stenosis in the same table. The mean difference in CC ratio of −0.26 (95% CI: −0.46 to −0.06) between patients with and patients without AS was found to be statistically significant (P = .0134).

Multivariate logistic regression analysis was performed to predict severe AS by including the traditional variables age, sex, LVEF, BSA, Vmax, mean gradient, DI, AVA cm^2, and also the new variables OC and CC. Convergence of results was not reached, and none of the predictors were found to be significant in quasi-convergent results. Separate multivariate analysis was also performed using the traditional variables and separately using the two new variables to predict severe AS. Neither of these analyses resulted in any significant predictors possibly due to multicollinearity between these predictors. However, application of variable selection methods backward elimination, forward selection, and stepwise methods consistently resulted in two significant predictors: the traditional AVA cm^2 with OR 11.075 (95% CI: 1.899-64.58, P = .0075) and the new variable CC ratio with OR 0.024 (95% CI: 0.002-0.378, P = .0079). These results can be found in Table 2.

Predictive performance of the multivariate logistic regression for the presence or absence of severe AS with 2 predictors recommended by the variable selection methods was compared with selective models of various subsets of predictors one at a time using the measure receiver operating characteristic (ROC) area.

Table 3 includes summary of the results including ROC area estimate, its standard error, and the 95% confidence interval computed by the bootstrap sampling. The predictive performance measure ROC area of the model with the traditional AVA cm^2 variable was only 0.6934 (95% CI: 0.5387-0.8481). This number is relatively small compared with the ROC area of any model in Table 3. The model with AVA cm^2 and CC ratio was found to be the best model according to the predictive performance measure ROC area 0.8352 (95% CI: 0.7161-0.9542) compared with the model with any subset of variables. At most two predictors were included in these models because including any additional predictors did not result in significantly higher predictive performance.

Often standard echocardiographic numerical measures dichotomize AS as severe or nonsevere. It is fitting to identify a robust threshold value to dichotomize the numerical CC ratio value. The distribution plots in Figure 4 of CC ratio by severe and nonsevere AS groups illustrate the difference between them. Mainly the CC ratio

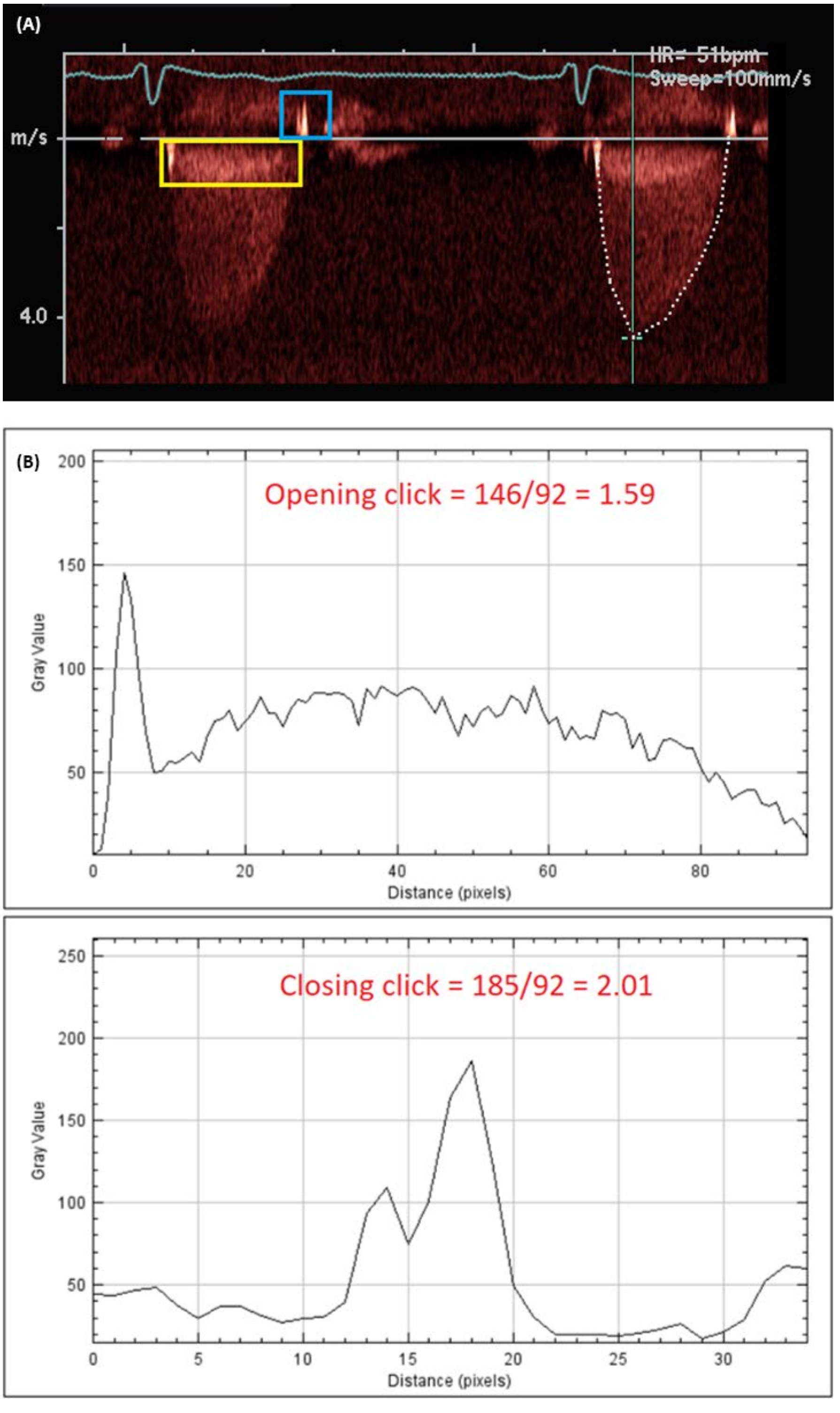

FIGURE 2 Continuous-wave Doppler, pixel intensity histograms, and ratios. (A) CW Doppler of patient with suspected AS with visible OC and CC demonstrating the areas of interrogation for OC (yellow) and CC (blue). (B) ImageJ analysis of signal intensity for areas of interrogation for OC (top panel) and CC (bottom panel). In this patient, the OC ratio was 1.59 and the CC ratio was 2.01

values of severe AS patients with a mean value of 0.9 (*SD* = 0.30) are lower than 1 but the values overlap with nonsevere AS patients.

To obtain a robust threshold for CC ratio to classify severe AS from nonsevere AS, sensitivity analysis was performed. Lower CC ratio threshold value ranging 0.80-0.84 revealed 100% specificity. In the study group of 48 patients, four patients had CC ratios in the 100% specificity range in whom standard echo criteria did not indicate severe AS but cardiac catheterization did reveal severe AS. In these patients, CC ratio could change the classification of AS severity. Using current data with a CC ratio of 0.95, 62% specificity and 66% sensitivity can be obtained. We propose a threshold value of 0.95 for CC ratio to screen a patient for severe AS. A convenient threshold value for CC ratio would be 1.

To further identify the effectiveness of a binary CC threshold value of 0.95, we compared the predictive accuracy of three logistic regression models to distinguish severe AS from nonsevere AS. The ROC curve area estimate was used as the measure of predictive accuracy of the model. We measured the difference between ROC curve area

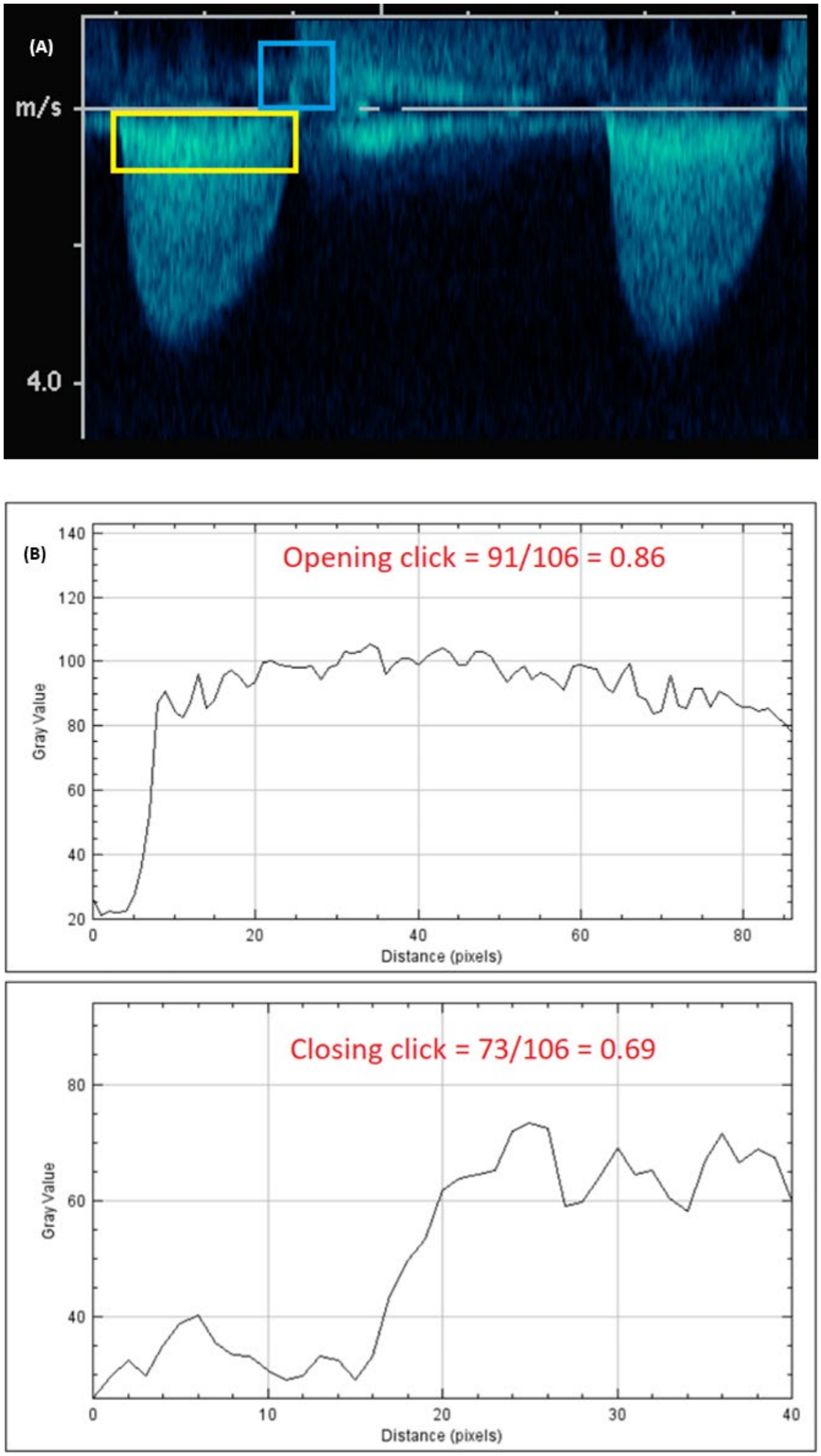

FIGURE 3 Continuous-wave Doppler, pixel intensity histograms, and ratios. (A) CW Doppler of patient with suspected AS with no visible OC or CC, using the same areas of interrogation for OC (yellow) and CC (blue) as in Figure 2. (B) ImageJ analysis of signal intensity for areas of interrogation for OC (top panel) and CC (bottom panel). In this patient, the OC ratio was 0.86 and the CC ratio was 0.69

estimates of a proposed model and the reference model that includes only AVA cm^2 as a predictor. Results are summarized in Table 4. We found that adding either numerical or dichotomized CC using the threshold of 0.95 to the model with AVA cm^2 would improve the predictive accuracy of the model. The increase in the predictive accuracy of the model by adding dichotomized CC to the AVA cm^2 is 0.1110 (95% CI: 0.038-0.184, *P* = .003). On average 11.1% more observations are correctly identified by the model with dichotomized CC and AVA cm^2 compared with the reference model that includes only AVA cm^2. The increase in the predictive accuracy of 0.1488 (95% CI: 0.008-0.276, *P* = .0381) is slightly higher and significant if numerical CC is added to the model, which includes only AVA cm^2.

TABLE 1 Clinical and echocardiographic characteristics of patients with and without catheterization proven aortic stenosis

Covariate	Aortic stenosis (35)	Nonaortic stenosis (13)	*P*-value	Odds ratio or Difference between two means (95% CI)
Age	69.31 ± 7.89	70 ± 11.65	.8443	0.69 (−5.30, 6.69)
Male gender	22 (63)	10 (76)	.3583	0.51 (0.12, 2.19)
LVEF	54.00 ± 14.49	56.54 ± 13.45	.5854	−2.54 (−11.84, 6.76)
BSA	1.89 ± 0.22	2.07 ± 0.28	.027	−0.18 (−0.35, 0.02)
V_{max}	15 (43)	1 (8)	.0363	9.00 (1.05, 77.03)
Mean gradient	13 (37)	2 (15)	.1484	3.25 (0.62, 17.01)
DI	20 (87)	3 (23)	.0358	4.44 (1.04, 19.01)
AVA cm^2	27 (77)	5 (38)	.0115	5.40 (1.38, 21.20)
OC	1.01 ± 0.31	1.20 ± 0.38	.0855	−0.19 (−0.41, 0.03)
CC	0.90 ± 0.31	1.16 ± 0.30	.0134	−0.26 (−0.46, −0.06)

Note: LVEF = left ventricular ejection fraction; BSA = body surface area; Vmax = maximum velocity; DI = dimensionless index; AVA cm^2 = aortic valve area; OC = opening click ratio; CC = closing click ratio.

TABLE 2 Multivariate logistic regression analysis with variables selected by backward elimination method

Parameter	Estimate	Standard error	Chi-square test statistics	*P*-value	OR (95% CI)
Intercept	4.7243	1.5966	8.7558	.0031	
AVA cm^2	1.2023	0.4498	7.1444	.0075	11.075 (1.899, 64.58)
CC	−3.7189	1.4007	7.049	.0079	0.024 (0.002, 0.378)

TABLE 3 ROC association statistics of logistic regression with different subsets predictors

Subsets of predictors	ROC area	Standard error	95% Wald confidence limits	
Aortic valve area	0.6934	0.0789	0.5387	0.8481
Aortic valve area and mean gradient	0.7154	0.0911	0.5369	0.8939
Aortic valve area and dimensionless index	0.7176	0.0838	0.5533	0.8819
Aortic valve area and maximum velocity	0.7824	0.0729	0.6396	0.9252
Aortic valve area and opening click	0.7912	0.0742	0.6457	0.9367
Aortic valve area and closing click	0.8352	0.0607	0.7161	0.9542

4 | DISCUSSION

As stated in the introduction, the combination of data utilizing traditional echo methods to determine the severity of AS is not always in agreement as shown in Table 1 and may require additional diagnostic procedures to assist in the evaluation of AS. This study describes a new quantitative method which further analyzes traditionally acquired Doppler data to assist in determining the severity of AS and possibly avoid additional diagnostic procedures. The method utilizes freely available offline software (ImageJ) which measures the LCD luminance of the spectral Doppler waveform selecting the relative intensity of OC and CC ratios as an indicator of AS severity. When the click information is added to standard echocardiographic parameters, incremental value is added to the determination of the severity of AS. We found that when the relative intensity of the CC ratio was 1 or less, there is net improvement in AS classification which may confer significant power to the clinician in cases of clinical ambiguity or contradictory data. In our patient population, the use of the CC ratio resulted in an additional 4 patients being correctly identified as having severe AS.

The Pearson correlation between numerical CC ratio and numerical echo AVA cm^2 is positive but not statistically significant (r = 0.064, P = .6414) and it is possible that rapid deceleration of red cells has some additional useful information about severe AS which is not available in echo measurement of the AVA.

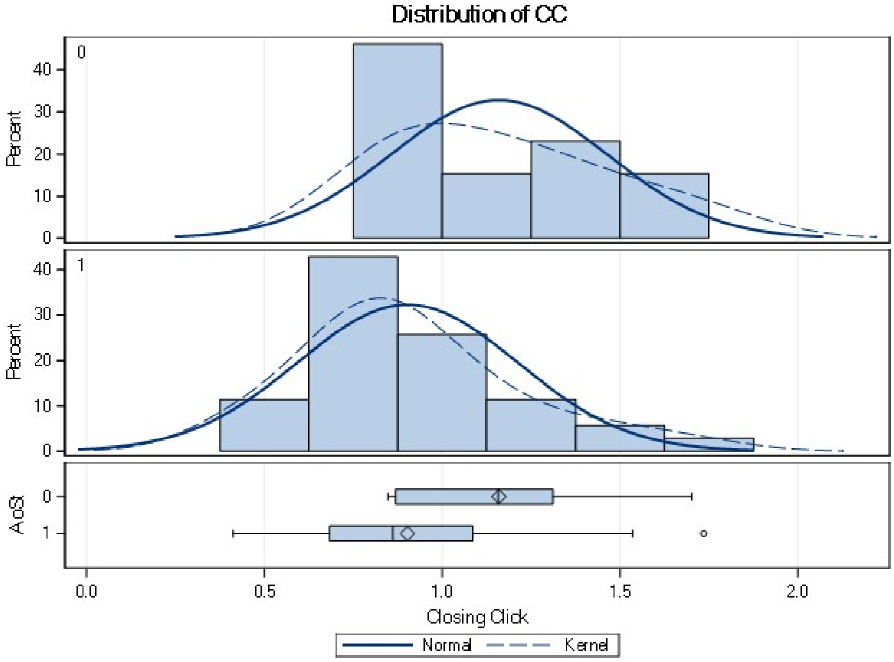

FIGURE 4 Distribution of CC among patients without and with catheterization proven aortic stenosis. Top panel: Number of patients without AS (vertical bars) as related to CC values (blue solid line). Dotted blue line represents normal distribution. Middle panel: Number of patients with AS (vertical bars) as related to CC values (blue solid line). Dotted blue line represents normal distribution. Bottom panel: Mean values of CC are different for patients without AS (top bar) and those with AS (bottom bar). Often standard echocardiographic numerical measures are dichotomized to identify the presence of severe AS binary value. It is fitting to identify a robust threshold value to dichotomize the numerical CC value. The distribution plots in Figure 4 of CC by severe and nonsevere AS groups illustrate the difference between them. Mainly the CC values of severe AS patients with mean 0.9 (*SD* = 0.30) are lower and lower than 1 but the values overlap with nonsevere AS patients. Descriptive statistics of CC values by severe AS groups can be found in Table I supplement. Central illustration: Central Illustration schematically shows the addition of the pixel density histogram with intensity ratios may assist standard imaging in the diagnosis of severe aortic stenosis. OC represents opening click, and CC represents closing click

Monitoring CW Doppler clicks ratios may act as a warning signal of a diminishing aortic valve area:

It seems that CC ratio was more precise than OC ratio in determining the severity of AS may correlate with a diminished auscultatory A2 predictive of severe AS.

4.1 | Study limitations

There is a clear limitation in the small sample size of this study. In the case of low flow, low gradient AS the clinical scenario can be challenging and the use of Doppler clicks may help distinguish pseudo-severe AS from true mechanical obstruction but the dataset is under powered for this analysis.[15] These patients may be worth evaluating in a further study. The gold standard used to determine the severity of AS was cardiac catheterization with its use of gradients and cardiac output. Thermodilution was used in the majority of cases (67%) to calculate cardiac output. The degree of tricuspid regurgitation was not noted, which could affect the accuracy of thermodilution cardiac output. For cases in which the Fick calculation was used to determine cardiac output, assumptions inherent in the formula decrease the reliability of cardiac catheterization as a gold standard. Aortic valve closing click intensity may reflect the degree of valve calcification and leaflet mobility. In this study, the Agatston score was not determined and a calcification score may also be a useful determinant of AS severity and could be correlated with click ratios.[16]

5 | CONCLUSION

Understanding of the importance of auscultatory aortic valve opening and closing sounds and analyzing their spectral Doppler equivalent leads to a new predictor of severe AS. The pixel density histogram of the aortic valve spectral Doppler waveform which accomplishes this analysis is not a current standard echocardiographic procedure. It is potentially a useful addition for software to be incorporated into echocardiographic machines and reading stations, and may be the basis for further research.

6 | PERSPECTIVES

6.1 | Clinical competencies

Understanding the importance of aortic valve opening and closing sounds and its spectral Doppler equivalent may assist in the

TABLE 4 Comparison between three models to predict severe AS using ROC curve area estimates

	Contrast between (Model i) and (Model j)	Difference between two ROC curve area Estimates	Standard error	95% Confidence Limits		Chi-square	*P*-value
(Binary CC and Binary AVA cm^2) and (Binary AVA cm^2)	0.1110	0.0374	0.038	0.184		8.810	.003
(Numerical CC and Numerical AVA cm^2) and (Binary AVA cm^2)	0.1088	0.0966	−0.081	0.298		1.268	.2602
(Numerical CC and Binary AVA cm^2) and (Binary AVA cm^2)	0.1418	0.0684	0.008	0.276		4.300	.0381
(Binary AVA cm^2) and (No predictors)	0.6934	0.0789	0.539	0.848		21.167	.0003

Note: Different models are identified by the subsets of the predictors in the first column. The model in the bottom row which includes the predictor binary AVA cm^2 is the reference model.

echocardiographic diagnosis of aortic stenosis. The creation of a pixel density histogram is a procedural skill of value to support this new echocardiographic marker.

6.2 | Translational outlook

Further studies should be performed to analyze aortic valve opening and closing sounds. The pixel density histogram of the aortic valve spectral Doppler waveform which accomplishes this analysis is not a current standard echocardiographic procedure. It is potentially a useful addition for software to be incorporated into echocardiographic machines and reading stations, and may be the basis for further research.

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