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RESEARCH ARTICLE

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Aortic closure signal length on doppler echocardiography differentiates aortic patient-prosthesis mismatch from prosthetic stenosis

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Abstract

Purpose: The purpose of this study was to investigate the diagnostic potential of the aortic closure (A2) signal length on Doppler echocardiography in distinguishing aortic patient-prosthesis mismatch (PPM) from prosthetic stenosis among patients with elevated gradients over bioprosthetic valves.

Methods: The A2 signal length was retrospectively measured for 150 patients with bioprosthetic aortic valves (50 with PPM, 50 with prosthetic stenosis, and 50 with normally functioning valves) from transthoracic echocardiograms performed at NYU Langone Health between 01/01/2012 and 08/01/2018.

Results: Mean A2 signal length was shorter among patients with PPM (11.1 ms ± 5.2 ms), than among those with prosthetic stenosis (21.1 ms ± 6.0 ms), $P < .001$ and controls (21.7 ms ± 7.4 ms), $P < .001$. There was no difference in A2 signal length between prosthetic stenosis and controls. The A2 signal length yielded an AUC of 0.89 (95% CI 0.82-0.95) for predicting PPM over prosthetic stenosis.

Conclusion: Among patients with bioprosthetic aortic valves, the length of the A2 signal on Doppler echocardiography is shorter in PPM than in prosthetic stenosis and normally functioning valves. The A2 signal length may represent a novel metric to distinguish PPM from prosthetic stenosis.

KEYWORDS
A2 signal, aortic stenosis, bioprosthetic valve, doppler echocardiography, patient-prosthesis mismatch

1 | INTRODUCTION

By nature of their design, prosthetic aortic valves are almost always obstructive to some degree compared to native aortic valves,[1] resulting in higher resting jet velocity across the valve. However, peak prosthetic aortic jet velocities elevated to greater than 3 m/s are considered abnormal.[2] The most common etiology of abnormally elevated flow velocities is patient-prosthesis mismatch (PPM),[2] a condition where the effective orifice area (EOA) of the prosthetic valve is small in relation to the patient's body surface area (BSA).[3] The principal hemodynamic consequence of this condition is that elevated gradients through a normally functioning prosthetic valve are required to maintain an adequate cardiac output.[3,4] PPM can be determined using Doppler echocardiography by applying the simplified continuity equation to calculate the EOA and indexing this to BSA.[5] The resulting indexed EOA (iEOA) has been inversely associated with elevated gradients in a curvilinear relationship, with an iEOA$\leqslant$0.85 cm^2/m^2 considered the threshold for PPM in the aortic position.[3,6] PPM can be further classified as moderate (iEOA 0.65-0.85 cm^2/m^2) or severe (iEOA <0.65 cm^2/m^2).[4] The estimated overall prevalence of PPM after

aortic valve replacement (AVR) is 44%,[7] and it has been associated with a range of adverse clinical outcomes. There is a strong and independent relationship between iEOA and the extent of left ventricular (LV) mass regression, which can result in persistent LV hypertrophy and a significant reduction in cardiac index after AVR, with the greatest reductions seen in the most severe cases of PPM.[3] It has also been associated with structural valve deterioration.[8] Overtime, this leads to reduced exercise tolerance and functional recovery, and can result in symptoms from systolic and/or diastolic dysfunction.[3,9] PPM has been independently associated with both heart failure and late mortality following AVR.[10,11]

However, an elevated peak prosthetic aortic jet velocity (> 3 m/s) can also be caused by an acquired stenosis of the prosthetic valve, which can result from leaflet degeneration.[2] The current algorithm published in the American Society of Echocardiography Guidelines uses echocardiographic data for the patient's acceleration time in addition to the shape of the jet over the prosthetic valve (ie, early or late peaking) to differentiate PPM from prosthetic stenosis.[1] Nevertheless, differentiating the two remains challenging. The aim of this study was to investigate the difference in the length of the aortic closure (A2) signal on doppler echocardiography between patients with PPM and patients with prosthetic stenosis.

2 | METHODS

This is a retrospective study conducted at NYU Langone Health with IRB approval. The Syngo Echocardiography Database (Siemens Healthineers, Erlangen, Germany) was used to identify all consecutive echocardiograms performed at NYU Langone Health between January 1, 2012 and August 1, 2018. Echocardiograms selected for inclusion in this study were for patients age > 18 years old with a bioprosthetic aortic valve with complete Doppler imaging available for review. Patients were excluded if they had a mechanical aortic valve or did not have body surface area and aortic valve peak gradient data available. Duplicate patients were excluded. Among all consecutive echocardiograms meeting these criteria, patients with prosthetic aortic valve peak gradient >36 mmHg (ie, peak prosthetic aortic jet velocity > 3 m/s) were identified (a total of 923 echocardiograms).

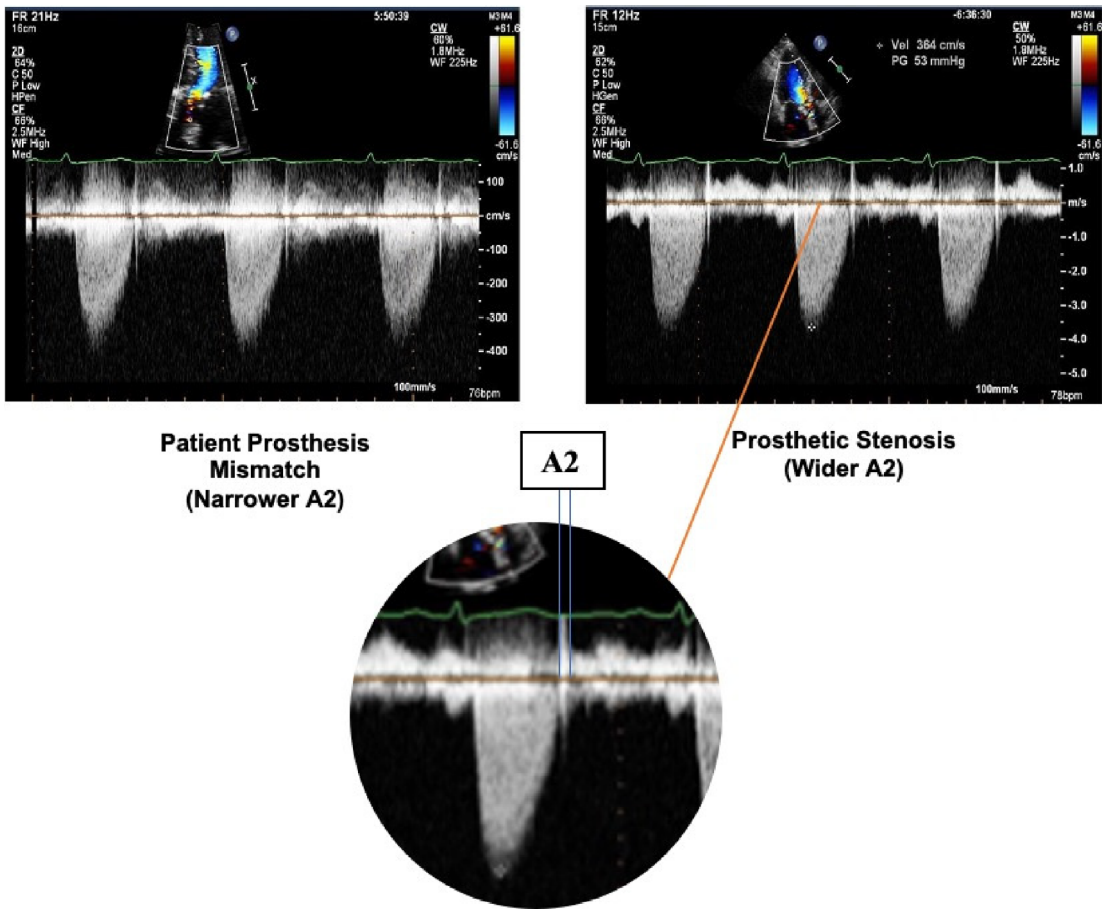

FIGURE 1 Representative doppler echocardiography images of aortic closure signal (A2) length in a patient with patient-prosthesis mismatch and a patient with prosthetic stenosis. A2 signal length was measured from the beginning of the doppler signal to the end (ie, maximum signal length), as annotated [Color figure can be viewed at wileyonlinelibrary.com]

Patients were identified as having prosthetic stenosis and PPM using the echocardiographic report, or, if no diagnosis was specified, American Society of Echocardiography diagnostic criteria[1] were used. These criteria differentiate prosthetic stenosis from PPM among patients with peak prosthetic aortic jet velocity > 3 m/s using the dimensionless index, jet contour, and acceleration time. Fifty echocardiograms with the highest prosthetic aortic valve peak gradients from each group (prosthetic stenosis and PPM) were selected for inclusion in this study (100 echocardiograms total). Fifty age- and sex-matched patients with normally functioning bioprosthetic aortic valves were selected for the control group. In this selection process, two total patients were excluded for poor quality imaging and an inability to discern an A2 signal. In these cases, the patient with the next highest gradient was selected for inclusion.

Each of the 150 echocardiograms was reviewed within the Syngo Echocardiography Database. The A2 signal length and acceleration time were measured for each patient on continuous wave Doppler recordings, using a ruler tool to measure from the start of the A2 Doppler signal to the end (ie, maximum signal length) at the baseline. The Doppler envelope with the clearest demarcation between the beginning and end of the A2 was chosen. Figure 1 demonstrates representative images from the PPM and prosthetic stenosis groups, with annotations for A2 signal length. Twenty randomly selected echocardiograms (10 from the PPM group and 10 from the prosthetic stenosis group) were sent to a board-certified echocardiographer (Adam H. Skolnick) for measurement of the A2 signal length to assess inter-observer reliability. Both study members (Thara Ali and Adam H. Skolnick) were blinded to study group for measurement of A2. Data for age, sex, blood pressure, heart rate, left ventricular ejection fraction (LVEF), aortic valve peak gradient, left ventricular end-diastolic diameter, and aortic root diameter were extracted from the echocardiogram report. Indexed effective orifice area was calculated by indexing the patient's valve size to their body surface area.

2.1 | Statistical analysis

Continuous variables were represented as mean ± SD when following a normal distribution and compared using two-sample *t* test, or as median [interquartile range] and compared using non-parametric Mann-Whitney *U* test when following a non-normal distribution. Dichotomous variables were compared using a chi-square test. A multivariate linear regression analysis was used to adjust for potential confounders in the relationship between PPM and A2 signal length. Sensitivity and specificity of the A2 signal length for PPM were calculated based on an A2 signal length of less than 15 ms. A receiver operating characteristic (ROC) curve analysis with a 95% confidence interval (CI) was generated to assess the performance of the A2 signal length in differentiating PPM and prosthetic stenosis. A Pearson's correlation test was used to assess for a linear association between EOA_i and A2 signal length. A *P* value <.05 was considered statistically significant. All analyses were performed in Stata statistical software Release 14 (StataCorp, College Station, Texas).

TABLE 1 Clinical Characteristics of patients with patient-prosthesis mismatch, prosthetic stenosis, and controls

	PPM N = 50	Prosthetic stenosis N = 50	Control N = 50	*P* value PPM vs controls	*P* value prosthetic stenosis vs Controls	*P* value PPM vs prosthetic stenosis
Demographics						
Age (years)	69 [61-81]	72 [64-86]	75 [66-86]	.07	.38	.47
Female sex	25 (50%)	25 (50%)	25 (50%)	1.00	1.00	1.00
Systolic blood pressure (mm Hg)	136 [120-160]	126 [118-143]	126 [117-147]	.08	.88	.05
Diastolic blood pressure (mm H)	73 [64-81]	70 [60-77]	73 [63-82]	.65	.24	.10
Heart rate(BPM)	64 ± 12	70 ± 15	75 ± 17	.001	.08	.07
TTE data						
iEOAi (cm^2/m^2)	0.5 [0.4-0.6]	0.4 [0.3-0.5]	1.2 [0.9-1.4]	<.0001	<.0001	<.0001
LVEF (%)	65 ± 11	59 ± 16	58 ± 15	.01	.33	.05
Aortic valve peak gradient (mmHg)	55 [48-61]	76 [69-97]	9 [6-12]	<.0001	<.0001	<.0001
LVEDD (cm),	4.5 [4.1-5.2]	4.4 [3.8-5.1]	4.3 [3.8-5.0]	.10	.40	.45
Aortic root diameter (cm),	3 [2.7-3.3]	3 [2.7-3.3]	2.9 [2.5-3.3]	.16	.17	.93
Acceleration time (ms)	91 [75-98]	123 [113-141]	95 [81-103]	.11	<.0001	<.0001

Note: Baseline demographic and clinical data of patients with aortic patient-prosthesis mismatch (PPM), aortic prosthetic stenosis and a control group with normally functioning Bioprosthetic aortic valves. Data are reported as number (percentage), mean ± SD, or median [interquartile range].
Abbreviations: iEOA, indexed effective orifice area; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

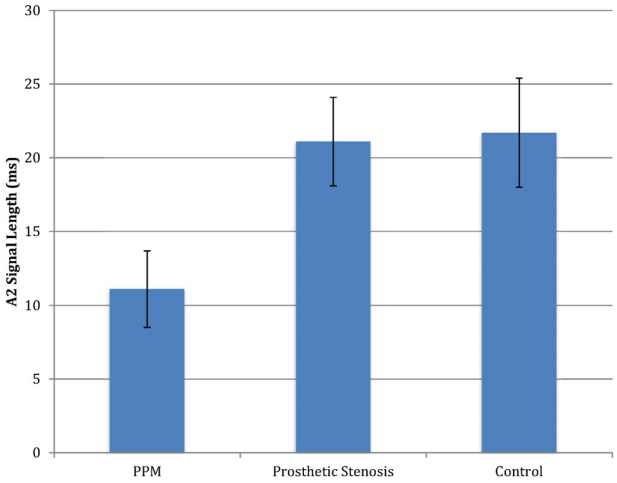

FIGURE 2 Mean aortic closure (A2) signal length ± SD as measured on continuous wave doppler echocardiography for patients with aortic patient-prosthesis mismatch (PPM), aortic prosthetic stenosis, and controls with normally functioning bioprosthetic aortic valves. Mean A2 signal length was lower in patients with PPM (11.1 ms ± 5.2 ms) than in those with prosthetic stenosis (21.1 ms ± 6.0 ms), $P < .001$ and in the control group (21.7 ms ± 7.4 ms), $P < .001$. There was no significant difference in A2 signal length between the prosthetic stenosis and control groups [Color figure can be viewed at wileyonlinelibrary.com]

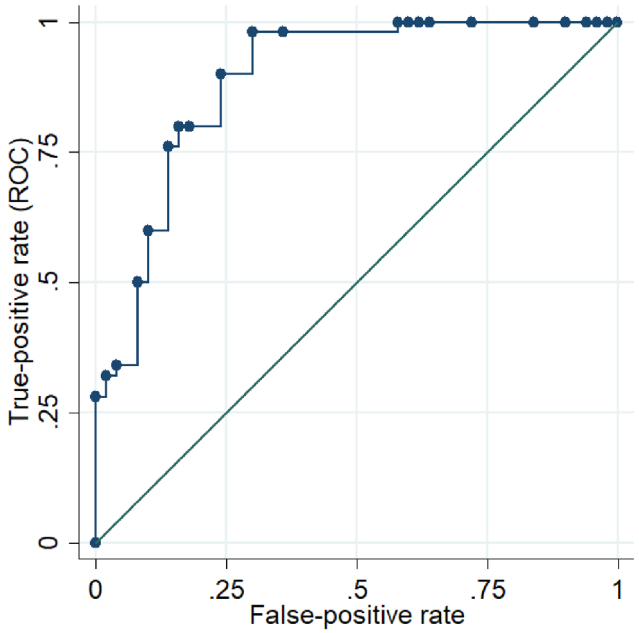

FIGURE 3 Receiver operating characteristic curve for aortic closure signal (A2) length in predicting patient-prosthesis mismatch over prosthetic stenosis. The A2 signal length is associated with an AUC of 0.89 (95%, CI 0.82-0.95) for predicting PPM over prosthetic stenosis and controls [Color figure can be viewed at wileyonlinelibrary.com]

2.2 | Ethics statement

Ethics approval and consent to participate: This study was approved by the NYU IRB and a waiver for consent was obtained due to the retrospective nature of the analysis.

3 | RESULTS

No difference was observed in age or sex among patients with PPM, prosthetic stenosis, and the control group (Table 1). Mean A2 signal length was significantly shorter among patients with PPM (11.1 ms ± 5.2 ms) than among those with prosthetic stenosis (21.1 ms ± 6.0 ms), $P < .001$ and the control group (21.7 ms ± 7.4 ms), $P < .001$ (Figure 2). There was no difference in A2 signal length between the prosthetic stenosis and control groups.

There were differences in the echocardiographic features among the three groups studied (Table 1). PPM, prosthetic stenosis, and the controls differed from one another in their iEOA ($P < .0001$) and aortic valve peak gradient ($P < .0001$). Patients with prosthetic stenosis had a significantly longer acceleration time than either the PPM or control group ($P < .0001$). PPM patients had lower heart rates and higher LVEF than the controls ($P = .001$ and $P = .01$, respectively). Given these population differences, a multivariate linear regression analysis was performed assessing the significance of the difference in A2 signal length between the PPM and prosthetic stenosis groups adjusting for age, sex, aortic valve peak gradient, acceleration time, iEOA, LVEF and heart rate as potential confounders. The difference in A2 signal length between PPM and prosthetic stenosis remained significant after adjusting for these variables (beta = 11.7, $P < .001$). Interclass correlation coefficient to determine inter-observer reliability in measuring the A2 signal length was 0.944 (95% CI 0.857-0.978).

The A2 signal length was associated with an AUC of 0.89 (95%, CI 0.82-0.95) for predicting PPM over prosthetic stenosis (Figure 3). At a threshold of less than 15 ms, the A2 signal length had a sensitivity of 82% and a specificity of 80% for predicting PPM over prosthetic stenosis. There was no association between iEOA and A2 signal length by Pearson's correlation coefficient ($r = 0.11$, $P = .19$).

4 | DISCUSSION

The current guidelines published by the American Society of Echocardiography use acceleration time and aortic jet contour to aid in distinguishing PPM from prosthetic stenosis; however, distinguishing the two remains challenging. The A2 signal length represents a novel metric for distinguishing PPM from prosthetic stenosis and can be easily measured using transthoracic doppler echocardiography. To our knowledge, this is the first study to report a technique to measure A2 signal length and the first to document the association of shorter A2 signal length with PPM.

It is unclear what causes a shorter A2 signal length in PPM compared to prosthetic stenosis and normally functioning bioprosthetic valves. Previous studies demonstrate that the actual closure of the aortic valve is silent, and that the A2 sound begins a few milliseconds after valve closure, likely due to vibrations of

cardiac structures.[12] It is possible that the relatively small size of the bioprosthetic aortic valve in patients with PPM produces lower amplitude vibrations of the cardiac structure following closure of the aortic valve, resulting in a shortened A2 signal compared to larger valves (ie, without PPM). However, we found no association between iEOA and A2 signal length. So, if a difference in vibration of the cardiac structures could explain the difference in A2 signal length, this difference would have to be caused by more than just the size of the valve. There may also be an impact of the rapid pressure recovery in the aorta in PPM, or differences in turbulent flow distal to the valve, that could affect the duration of the vibration caused by leaflet closure.[13] In theory, if the A2 signal length is a reflection of vibration of cardiac structures, a difference in left ventricular end-diastolic diameter (LVEDD) across groups could contribute to differences in measured A2 signal length. However, this was controlled for as there was no significant difference in LVEDD across our three groups. Given that the A2 signal length was similar in normally functioning and stenotic valves, it is unlikely that the longer A2 signal length observed in prosthetic stenosis compared to PPM was related to differences in leaflet thickness.

There are several limitations to this study. The main limitation is the relatively small sample size. The present analysis is focused upon patients with the highest peak gradients in the PPM and prosthetic stenosis groups for proof of concept using the most extreme examples. Although there was no interaction effect based on peak gradient, the magnitude of the observations in this study may differ in patients with lower peak gradients. While visual assessment of leaflet motion is another method for subjectively differentiating PPM and prosthetic stenosis, it was not included in this analysis given the presence of variable imaging quality precluding visualization of the leaflets in many cases. There is no true gold standard for differentiating PPM from prosthetic stenosis with which to compare the A2 signal length. Given our small sample size, there is a potential for overfitting in our multivariate linear regression analysis. Finally, not every patient has a distinct A2 closure signal, and some of the most severe cases of prosthetic stenosis may have an absent A2 altogether.

5 | CONCLUSION

In conclusion, the A2 signal length on Doppler echocardiography is shorter among patients with PPM than among patients with prosthetic stenosis and controls with normally functioning bioprosthetic aortic valves. The A2 signal length may represent a novel measurement that can be used clinically to differentiate PPM from prosthetic stenosis and warrants validation in a larger dataset.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests related to this current study.

AUTHORS CONTRIBUTIONS

Thara Ali, Michael S. Garshick and Adam H. Skolnick contributed substantially to study design, concept and writing of the manuscript. MS made substantial contributions to data acquisition and interpretation of data as well as providing critical revisions of the manuscript.

DATA AVAILABILITY STATEMENT

The dataset used for the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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