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Doppler-Detected Valve Movement in Aortic Stenosis: A Predictor of Adverse Outcome

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ABSTRACT

Background: The absence of auscultatory aortic valve closure sound is associated with severe aortic stenosis. The absence of Doppler-derived aortic opening (A_{op}) or closing (A_{cl}) may be a sign of advanced severe aortic stenosis.

Hypothesis: Absent Doppler-detected A_{op} or A_{cl} transient is indicative of very severe aortic stenosis and is associated with adverse outcome.

Methods: A total of 118 consecutive patients with moderate (n = 63) or severe aortic stenosis (n = 55) were included. A_{op} and A_{cl} signals were identified in a blinded fashion by continuous-wave Doppler. Patients with and without A_{op} and A_{cl} were compared using χ^2 test for dichotomous variables and analysis of variance for continuous variables. The associations of A_{op} and A_{cl} with aortic valve replacement were determined.

Results: A_{op} or A_{cl} were absent in 22 of 118 patients. The absence of A_{op} or A_{cl} was associated with echocardiographic parameters of severe aortic stenosis. The absence of A_{op} or A_{cl} was associated with incident aortic valve replacement (36.4% vs 7.3%, respectively, $P < 0.001$). Even in patients with aortic valve area $<1\,cm^2$, the absence of A_{op} or A_{cl} was still associated with increased rate of aortic valve replacement (42.1% vs 13.9%, respectively, $P = 0.019$) and provided incremental predictive value over peak velocity.

Conclusions: In a typical population of patients with aortic stenosis, approximately 1 in 6 has no detectible aortic valve opening or closing Doppler signal. The absence of an A_{op} or A_{cl} signal is a highly specific sign of severe aortic stenosis and is associated with incident aortic valve replacement.

Introduction

Severe aortic stenosis has well-established clinical and echocardiographic features.[1–5] Although parameters such as aortic jet velocity, rate of disease progression, blood pressure response to exercise, the presence of left ventricular hypertrophy, and B-type natriuretic peptide predict outcomes,[6–13] management is largely based on the presence of symptoms or decreased left ventricular systolic function.[14]

On auscultation, severe aortic stenosis is associated with a diminished or absent aortic component of the second heart sound.[5] Because Doppler echocardiography produces distinct aortic opening (A_{op}) and aortic closing (A_{cl}) transients in patients without aortic stenosis (Figure 1),[15] the lack of A_{op} or A_{cl} (Figure 2) may represent impaired valve excursion and may be associated with severe aortic stenosis. Therefore, we hypothesized that absent a Doppler-derived A_{op} or A_{cl} transient is a marker of severe aortic stenosis and predicts adverse outcome. The goal of this study was to examine the association of the absence of Doppler-derived A_{op} or A_{cl} with outcomes in patients with moderate and severe aortic stenosis.

Methods

We retrospectively reviewed the echocardiogram database of the Kaiser Permanente Medical Center at Redwood City, California, to identify all patients with moderate or severe aortic stenosis who had been studied between January 2007 and October 2010. Among those identified, we excluded patients with prosthetic aortic valves and those with more than mild aortic regurgitation.

Standard echocardiograms were performed using the Acuson Sequoia (Acuson, Mountain View, CA) or GE Vivid 5 (GE Healthcare, Milwaukee, WI) ultrasound systems. All patients underwent a comprehensive examination that included M-mode, 2-dimensional (2-D) echocardiography, color Doppler, pulse-wave Doppler, continuous-wave

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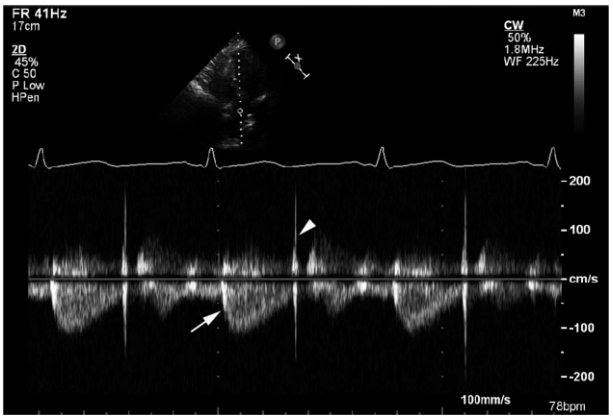

Figure 1. Continuous-wave Doppler of normal aortic valve showing presence of aortic opening (arrow) and aortic closing (arrowhead).

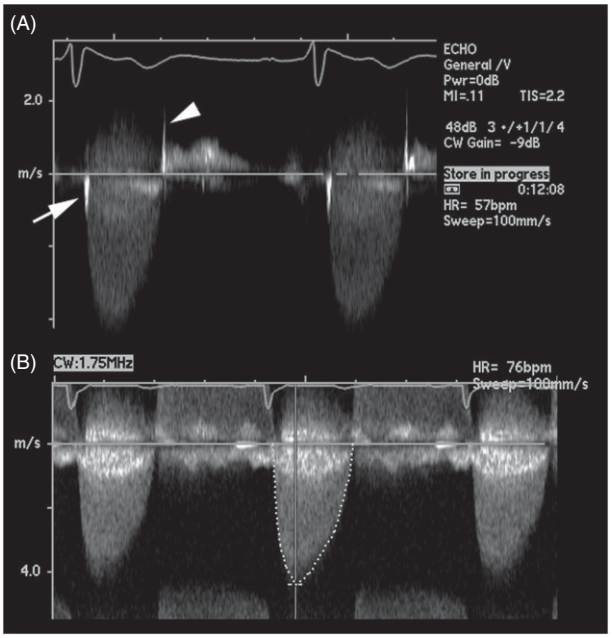

Figure 2. (A) Continuous-wave Doppler of stenotic aortic valve showing presence of aortic opening (arrow) and aortic closing (arrowhead). (B) Continuous-wave Doppler of stenotic aortic valve showing absence of aortic opening and aortic closing. Note the similar jet velocities of these patients.

Doppler, and nonimaging Doppler according to recommended methods.[16] Multiple transducer positions were used to record peak aortic jet velocities. Aortic valve area was calculated using the continuity equation.[17] Left ventricular ejection fraction was measured quantitatively using the 2-D echocardiography biplane method of disks.[18] Severe aortic stenosis and moderate aortic stenosis were defined based on published guidelines.[14] Doppler A_{op} and A_{cl} transients derived from echocardiograms were reviewed by an experienced cardiologist (XR) blinded to clinical and other echocardiographic data. A subset of echocardiograms was independently verified by a second cardiologist (NMB), and interobserver agreement was calculated using kappa statistics.

After identification and echocardiographic measurement of the study group, clinical, laboratory and outcome data were obtained by chart review. The Kaiser Permanente electronic medical record system includes progress notes, operative reports, discharge summaries, diagnoses, and robust problem lists. Coronary artery disease, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, left ventricular hypertrophy, heart failure, and stroke were recorded for each patient if the condition was present. The diagnosis of left bundle branch block or atrioventricular block was determined based on electrocardiographic interpretation.

The primary end point was aortic valve replacement. Secondary end points were hospitalization for heart failure and all-cause mortality. Hospitalization for heart failure was defined as hospital admission for a clinical syndrome involving at least 2 of the following: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary crackles, third heart sound, cardiomegaly on chest radiography, or pulmonary edema on chest radiograph. The study protocol complies with the Declaration of Helsinki and was approved by the institutional review board.

Differences in patient characteristics by presence of A_{op} and A_{cl} were determined using analysis of variance for continuous variables and χ^2 tests for dichotomous variables. Differences in outcome based on the presence of A_{op} and A_{cl} were determined using 2-sided χ^2 tests, with $P < 0.05$ defined as statistically significant. Analyses were performed using the Statistical Package for Social Sciences version 18.0 (IBM/SPSS, Chicago, IL). For these analyses, we report hazard ratios with 95% confidence intervals. A Kaplan-Meier plot aggregated cardiovascular events by date during follow-up for each group. Finally, we examined the incremental predictive value of the absence of A_{op} or A_{cl} beyond peak transaortic velocity by assessing the net reclassification index for both events and nonevents using the z score.[19]

Results

By keyword search of the echocardiography database, total of 121 patients were initially identified, of whom 3 were excluded (2 for prosthetic valve and 1 for moderate aortic regurgitation). Of the remaining 118 patients, 55 had severe aortic stenosis, and 63 had moderate aortic stenosis. Both A_{op} and A_{cl} were present in 96 patients, A_{op} was absent in 4, A_{cl} was absent in 7, and both A_{op} and A_{cl} were absent in 11. Thus, 22 had either A_{op} or A_{cl} absent. Of 10 randomly chosen Doppler tracings, there was excellent agreement between 2 cardiologists (kappa = 0.95).

Table 1 shows baseline characteristics for patients with both A_{op} and A_{cl} present vs A_{op} or A_{cl} absent. The 2 groups were similar except for the increased prevalence of severe aortic stenosis when A_{op} or A_{cl} was absent ($P < 0.0001$). Baseline echocardiographic parameters for patients with both A_{op} and A_{cl} present vs A_{op} or A_{cl} absent were significantly different, except for left ventricular ejection fraction and pulmonary artery systolic pressure (Table 2).

The mean follow-up after the index echocardiogram was 27 ± 13 months. Patients with A_{op} or A_{cl} absent had an increased rate of aortic valve replacement (36.4% vs 7.3%, respectively, $P < 0.001$) as compared with patients with

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Table 1. Baseline Clinical Characteristics for A_{op} and A_{cl} Present Versus A_{op} or A_{cl} Absent

Variable	A_{op} and A_{cl} Present, n = 96	A_{op} or A_{cl} Absent, n = 22	*P* Value
Age, y	79.2 ± 12	78.1 ± 11	0.666
Male gender	45 (46.9%)	13 (59.1%)	0.301
History			
Hypertension	81 (84.4%)	20 (90.9%)	0.431
Hyperlipidemia	73 (76.0%)	16 (72.7%)	0.745
Diabetes mellitus	24 (25.0%)	5 (22.7%)	0.823
Atrial fibrillation	29 (30.2%)	5 (22.7%)	0.485
Coronary artery disease	33 (34.4%)	7 (31.8%)	0.819
Heart failure	24 (25.0%)	3 (13.6%)	0.252
Stroke	9 (9.4%)	4 (18.2%)	0.234
Left bundle branch block	5 (5.2%)	2 (9.1%)	0.487
Atrioventricular block	12 (12.5%)	2 (9.1%)	0.656
LV hypertrophy	38 (39.6%)	7 (31.8%)	0.499
Medications			
β-Blocker	53 (55.2%)	15 (68.2%)	0.267
Diuretic	62 (64.6%)	13 (59.1%)	0.629
ACE-I/ARB	47 (49.0%)	14 (63.6%)	0.214
Statin	50 (52.1%)	16 (72.7%)	0.079
Aortic stenosis severity			
Moderate	57 (59.4%)	1 (4.5%)	
Moderate/severe	24 (25.0%)	1 (4.5%)	
Severe	15 (15.6%)	20 (91.0%)	<0.0001

Abbreviations: A_{cl}, aortic closing; ACE, angiotensin-converting enzyme; A_{op}, aortic opening; ARB, angiotensin receptor blocker; LV, left ventricular.

both A_{op} and A_{cl} present (Table 3). Even in patients with aortic valve area $<1\,cm^2$, the absence of A_{op} or A_{cl} was still associated with increased rate of aortic valve replacement (42.1% vs 13.9%, respectively, $P = 0.019$) (Table 4). When combining the end points of aortic valve replacement or heart failure hospitalizations in patients with aortic valve area $<1\,cm^2$, the absence of A_{op} or A_{cl} was associated with decreased event-free survival ($P = 0.04$) (Figure 3). Net reclassification index was 0 for events ($P = 1.0$) but was 0.097 for nonevents (2-sided $P = 0.02$, $z = 2.357$). Using the absence of A_{op} or A_{cl} to classify patients after initial stratification by peak transaortic jet velocity did not result in net improvement in predicting events. However, the presence of A_{op} and A_{cl} significantly improved prediction of nonevents (ie, improved specificity); negative predictive value was 0.93 for incident aortic valve replacement.

Table 2. Echocardiographic Characteristics for A_{op} and A_{cl} Present Versus A_{op} or A_{cl} Absent

Variable	A_{op} and A_{cl} Present, n = 96	A_{op} or A_{cl} Absent, n = 22	*P* Value
Peak gradient, mm Hg	48.9 ± 19	83.6 ± 13	<0.0001
Mean gradient, mm Hg	27.9 ± 12	51.3 ± 12	<0.0001
Aortic valve area, cm^2	1.04 ± 0.24	0.78 ± 0.17	<0.0001
Aortic valve area index, cm^2/m^2	0.553 ± 0.13	0.409 ± 0.10	<0.0001
V_{max}, m/s	3.4 ± 0.7	4.5 ± 0.5	<0.0001
Dimensionless ratio	0.31 ± 0.09	0.23 ± 0.05	<0.0001
LV ejection fraction, %	60 ± 9	63 ± 7	0.233
Pulmonary artery systolic pressure, mm Hg	39.7 ± 14	36.9 ± 13	0.451

Abbreviations: A_{cl}, aortic closing; A_{op}, aortic opening; LV, left ventricular; V_{max}, maximal transaortic jet velocity.

Table 3. Outcomes Comparing A_{op} and A_{cl} Present Versus A_{op} or A_{cl} Absent

Variable	A_{op} and A_{cl} Present, n = 96	A_{op} or A_{cl} Absent, n = 22	*P* Value
Mortality	14 (14.6%)	4 (18.2%)	0.672
Heart failure	8 (8.3%)	2 (9.1%)	0.908
Aortic valve replacement	7 (7.3%)	8 (36.4%)	<0.0001

Abbreviations: A_{cl}, aortic closing; A_{op}, aortic opening.

Table 4. Outcomes Comparing A_{op} and A_{cl} Present Versus A_{op} or A_{cl} Absent in Patients With Aortic Valve Area $<1.0\,cm^2$

Variable	A_{op} and A_{cl} Present, n = 36	A_{op} or A_{cl} Absent, n = 19	*P* Value
Mortality	8 (22.2%)	3 (15.8%)	0.571
Heart failure	3 (8.3%)	2 (10.5%)	0.788
Aortic valve replacement	5 (13.9%)	8 (42.1%)	0.019

Abbreviations: A_{cl}, aortic closing; A_{op}, aortic opening.

Discussion

Previous studies have found that physical examination findings of patients with severe aortic stenosis correlate with those of Doppler echocardiography.[1–4] In addition, Munt et al also found that auscultatory, single, second heart sound was predictive of increased risk of death or valve replacement. However, the association was no longer

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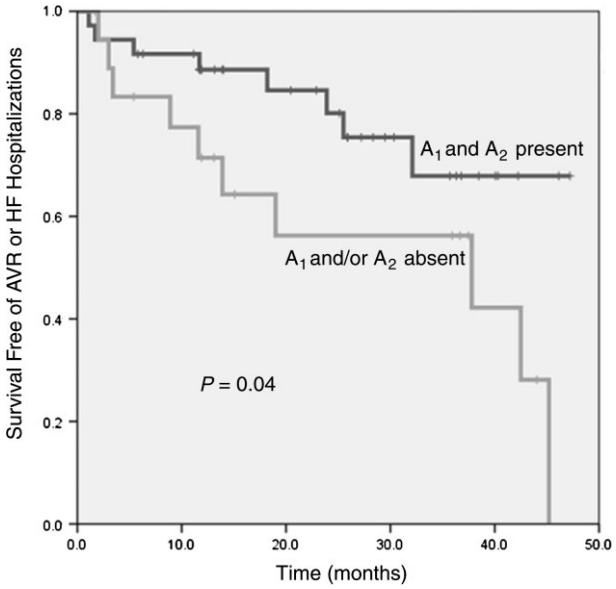

Figure 3. Survival free of aortic valve replacement (AVR) or heart failure (HF) hospitalizations in patients with aortic valve area $<1\,cm^2$. Abbreviations: A_1, A_{op}; A_2, A_{cl}.

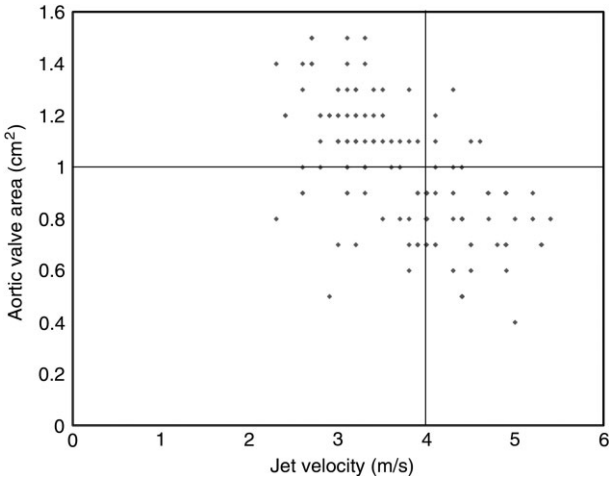

Figure 4. Scatter plot of patients with and without aortic opening (A_{op}) and aortic closing (A_{cl}). Blue points denote patients with A_{op} and A_{cl} present; red points denote patients with A_{op} or A_{cl} absent.

present after multivariate analysis.[1] In our study, not only did the absence of an A_{op} or A_{cl} signal predict incident aortic valve replacement in the overall population, it remained predictive in patients with aortic valve area $<1.0\,cm^2$. Thus, the absence of an A_{op} or A_{cl} signal is a robust sign of clinically significant aortic stenosis.

On auscultation, severe aortic stenosis is associated with diminished or absent aortic component of the second heart sound.[5] The physiologic mechanism is likely due to decreased valve excursion due to calcification and restricted leaflet motion. Because Doppler echocardiography produces distinct A_{op} and A_{cl} transients in patients without aortic stenosis,[15] the lack of A_{op} or A_{cl} signal in patients with severe aortic stenosis represents extremely reduced valve excursion. Although severe aortic stenosis is defined by transvalvular gradient, jet velocity, and valve area,[14] a spectrum of disease severity exists even within severe aortic stenosis patients. We believe that the lack of an A_{op} or A_{cl} signal represents a more severe degree of aortic stenosis (Figure 4), analogous to patients with very severe aortic stenosis as defined by jet velocity $\geq 5.5\,m/s$.[20]

Limitations

We believe the unique features of this study include its generalizability, blinded interpretation of Doppler signal, and thorough chart review facilitated by a robust electronic medical records system. Nonetheless, potential limitations include the single-center retrospective design. A second limitation is that our analytic sample was composed of patients with and without symptoms. A study of patients with asymptomatic severe aortic stenosis is under way to examine the predictive value of absent A_{op} or A_{cl} in that population. Third, our study sample size did not provide sufficient power to examine the predictive value of A_{op} and A_{cl} individually. Finally, patients in our study were significantly older than prior studies,[6,7,10] and our results may be not be applicable to younger patients.

Conclusion

We found that in a population of patients with moderate to severe aortic stenosis, 1 in 6 patients has no detectible aortic opening or closing Doppler signal by echocardiography. Furthermore, the absence of an A_{op} or A_{cl} signal is a highly specific sign of severe aortic stenosis and is associated with incident aortic valve replacement, even in patients with aortic valve area $<1\,cm^2$. Thus, the absence of an A_{op} or A_{cl} signal merits consideration to be included as a sign of clinically significant aortic stenosis.

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