Rate of Change in Aortic Valve Area During a Cardiac Cycle Can Predict the Rate of Hemodynamic Progression of Aortic Stenosis

Steven J. Lester, MD; Doff B. McElhinney, MD; Joseph P. Miller, MD; Juergen T. Lutz, MD; Catherine M. Otto, MD; Rita F. Redberg, MD

**Background**—The ability to predict the rate of hemodynamic progression in an individual patient with valvular aortic stenosis has been elusive. The purpose of the present study was to evaluate whether the rate of change in aortic valve area (AVA) measured during the ejection phase of a cardiac cycle predicts the rate of hemodynamic progression in patients with asymptomatic aortic stenosis.

**Methods and Results**—In 84 adults with initially asymptomatic aortic stenosis and a baseline AVA of ≥0.9 cm², annual echocardiographic data were obtained prospectively (mean follow-up 2.8±1.3 years). With the initial echocardiogram, the ratio of AVA measured at mid-acceleration and mid-deceleration to the AVA at peak velocity was calculated. The primary outcome variable was the annual rate of change in AVA (rate of progression), with rate of progression classified as rapid (a reduction in AVA of ≥0.2 cm²/y) or slow (<0.2 cm²/y). Rapid progression was significantly associated with an AVA ratio of ≥1.25 (P=0.004, risk ratio 3.1, 95% CI 1.2 to 7.9). The sensitivity, specificity, and positive predictive value of AVA ratio of ≥1.25 for the prediction of rapid progression of valvar aortic stenosis was 64%, 72%, and 80% respectively. The decrease in ejection fraction measured from the initial to final echocardiogram was small but greater for patients with an AVA ratio of ≥1.25 (−4±7% versus +2±7%, P<0.001).

**Conclusions**—A flow-dependent change in AVA can be measured during a routine transthoracic echocardiographic study. The rate of change in AVA is an additional measure of disease severity and may be used to predict an individual’s risk for subsequent rapid disease progression. *(Circulation. 2000;101:1947-1952.)*

**Key Words:** stenosis □ valves □ aorta □ echocardiography

The ability to predict the rate of progression of aortic stenosis in an individual patient has been elusive, yet clinically very important. In this cohort study, we evaluated the relationship between aortic valve dynamics measured with transthoracic Doppler echocardiography and the subsequent rate of stenosis progression. We found that in patients with mild or mild to moderate aortic stenosis, the rate of change in valve area measured during a cardiac cycle can be used to predict an individual’s risk for subsequent rapid aortic stenosis progression.

Valvular aortic stenosis is a progressive disease. For the population of patients, the rate of disease progression is related to the baseline severity of disease.1 On average, the aortic valve area (AVA) decreases by ~0.1 cm²/y, and the peak instantaneous gradient increases by 10 mm Hg/y.1–4 However, for an individual patient, there is marked variability with respect to the rate of hemodynamic progression.1–3,5 Therefore, an understanding of the mean rate of progression for the population of patients is of little value when trying to make a clinical decision for an individual patient.

The severity of aortic stenosis is generally determined with a calculation of AVA at only a single point in the cardiac cycle: the point of peak flow. However, during ejection, AVA is dynamic and Doppler echocardiography can be used to determine the valve area at each time point in the cardiac cycle. When aortic valve dynamics have been evaluated in patients with valvular aortic stenosis, it has been shown that the valve opens and closes more slowly than structurally normal valves.6,7 In addition, there appears to be no relationship between the rate of change in valve area during ejection and the usual indices of stenosis severity, such as AVA measured at peak velocity.7 Therefore, 2 patients with the same AVA, measured at peak velocity, may have very different valve dynamics. Although the maximum AVAs may be the same, a patient with a slower rate of change in valve area would have proportionately less time during ejection when the valve is maximally open and therefore the ventricle is more burdened by what may be considered more severe stenosis.

This was a cohort study of patients who were previously enrolled in a prospective analysis of aortic stenosis. We...
hypothesized that in patients with mild or mild to moderate valvular aortic stenosis, a slower rate of change in AVA measured during the ejection phase of a cardiac cycle would be related to an individual’s risk for subsequent rapid disease progression.

Methods

Patient Population
As described previously, 123 patients with asymptomatic valvular aortic stenosis referred by their primary care physician or cardiologist between September 1989 and April 1995 were enrolled prospectively.1 Entry criteria were (1) age of ≥21 years, (2) systolic murmur on auscultation, (3) no symptoms attributed to aortic stenosis, (4) aortic valve thickening with reduced systolic opening on 2-dimensional echocardiography, and (5) a maximum aortic jet velocity at rest of ≥2.5 m/s (2 SD > normal). Patients with a baseline AVA of < 0.9 cm² measured with the continuity equation (n=10) or an incomplete spectral Doppler envelope (n=29) were excluded. Data obtained prospectively for the remaining 84 patients were analyzed for the present study. Patients were not excluded on the basis of coexisting aortic regurgitation, mitral valve disease, hypertension, coronary artery disease, or comorbid noncardiac disease, because the goal was to have a sample representative of the clinical spectrum of disease. All subjects gave written informed consent.

Echocardiographic Data
A complete Doppler echocardiographic study was performed annually. Continuous-wave Doppler tracings were obtained from 3 windows (apical, right parasternal, and suprasternal) to obtain the maximum aortic jet velocity. Left ventricular outflow tract velocity was recorded from an apical approach with pulsed-wave Doppler echocardiography with a 5- to 10-mm sample volume length. Left ventricular outflow tract diameter was measured in mid systole from the parasternal long-axis view just proximal to the aortic leaflet insertion into the annulus. Maximum and mean pressure gradients were calculated with use of the Bernoulli equation, and AVA was calculated with use of the continuity equation.9 Ejection fraction was calculated according to the previously described biplane method of discs.9 Two-dimensional and Doppler echocardiographic data were recorded on videotape with the use of a commercially available ultrasound system. Representative Doppler tracings were selected and still-frame images were digitized with a Sequoia Ultrasound System (Acuson Corporation). Measurements were made from the digitized still images.

AVA was measured at different times during ejection according to a method previously reported, as described in detail here.10 From the continuous-wave Doppler profile, the peak velocity was measured. The time to half of the peak velocity during acceleration (1/2Δt) and deceleration (1/2Δt) was then determined. On the pulsed-wave Doppler profile from the left ventricular outflow tract, which had been obtained from a cardiac cycle with a similar ejection time (±10%) as the continuous-wave velocity profile, the velocities at 1/2Δt and 1/2Δt were determined (Figure 1). For all Doppler measurements, the average of at least 2 beats was used. The 3 pairs of velocities were then used to determine the ratio of the AVA at half-acceleration and half-deceleration to the valve area at peak velocity with the continuity equation:

![Figure 1](http://circ.ahajournals.org/content/101/8/1948/F1.large.jpg)
where AVA is the effective AVA, $p$ is peak velocity, $A_{LVOT}$ is left ventricular outflow tract area, $\cos \theta$ is the continuous-wave Doppler incidence angle, and $\cos \theta'$ is the pulsed-wave Doppler incidence angle. Because the aortic flow velocity at peak $V_{AO(p)}$ is by definition twice the velocity at half-acceleration $V_{AO(1/2a)}$, $V_{AO(p)}$ becomes $2V_{AO(1/2a)}$. Therefore, this equation can be simplified to:

$$\frac{AVA_{(2a)}}{AVA_{(p)}} = \frac{2A_{LVOT}(2a)}{A_{LVOT}(p)} = \frac{2}{\cos \theta'}$$

A similar equation can be used for the ratio of $AVA_{(1/2d)}/AVA_{(p)}$ (Md). With the expression of instantaneous AVA as a percentage of valve area at peak velocity, any errors caused through Doppler incidence angle and measurements of the LVOT area are eliminated.

To determine the rate of change in valve area, an AVA ratio (Md/Ma) was determined:

$$\frac{AVA_{(2a)}}{AVA_{(p)}} = \frac{2A_{LVOT}(2a)}{A_{LVOT}(p)} = \frac{M_d}{M_a}$$

Therefore, an individual with a slower rate of change in valve area during the ejection phase of a cardiac cycle will have a larger AVA ratio.

### Statistical Analysis

The outcome measure was the annual rate of change in AVA from the initial echocardiogram to the most recent follow-up echocardiographic measurement (total change in AVA divided by the duration of follow-up in years). This was analyzed both as a continuous variable and as an a priori defined dichotomous categorical variable, with the 2 groups composed of (1) patients with a decrease in AVA of at least 0.20 cm²/y (rapid progressors) and (2) patients with less of a decrease, no change, or an increase (slow progressors). Echocardiographic measures analyzed as independent variables for correlation with the rate of change in AVA included $AVA_{(1/2a)}$, $AVA_{(1/2d)}$, and AVA ratio (Md/Ma) as a continuous variable and a categorical variable ($<1.25$ or $\geq 1.25$). The ratio of 1.25 was chosen because it represented the median value of our sample population. The duration from the initial echocardiogram to the final follow-up echocardiogram was also analyzed as an independent variable for correlation with the rate of change of AVA. Correlation between continuous variables was tested with linear regression analysis. Fisher’s exact test or $\chi^2$ analyses were used to assess for significant correlation between dichotomous variables. Independent samples $t$ test was used to compare the mean values of continuous independent variables between two groups. Factors found to be significant on univariable analysis were entered into multivariable analysis with the use of forward stepwise multiple logistic regression. Unless otherwise specified, data are presented as mean±SD or as median and range. RR values with 95% CI are also presented. Intrarater and interrater variabilities in the measurement of the AVA ratio were evaluated in 10 randomly selected subjects. Variability was expressed as the mean±SD of the absolute difference between the two sets of measurements. SPSS for Windows version 7.0 (SPSS Inc) was used to perform statistical calculations.

### Results

#### Demographics

The mean age of the subjects was 63±15 years, and 54 (64%) were men. The duration of patient follow-up was 2.8±1.3 years (range 0.5 to 6.3 years).

<table>
<thead>
<tr>
<th>Rapid Progressors (n=48)</th>
<th>Slow Progressors (n=36)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, % male</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>65±12</td>
<td>62±14</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>158±51</td>
<td>150±54</td>
</tr>
<tr>
<td>PA systolic pressure, mm Hg</td>
<td>32±8</td>
<td>31±7</td>
</tr>
<tr>
<td>Moderate to severe AI, %</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Initial AVA, cm²</td>
<td>1.42±0.50</td>
<td>1.22±0.30</td>
</tr>
<tr>
<td>Maximum aortic jet velocity, m/s</td>
<td>3.5±0.5</td>
<td>3.7±0.6</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; PA, pulmonary artery; and AI, aortic insufficiency.

### Rapid Versus Slow Progression

There were no differences between rapid and slow progressors with respect to baseline demographic or hemodynamic parameters (Table). However, there were several factors related to AVA that differed between patients with rapid and slow progression. An AVA ratio of $\geq 1.25$ was associated with rapid progression ($P=0.004$, risk ratio [RR] 3.1, 95% CI 1.2 to 7.9). The sensitivity, specificity, and positive predictive value of AVA ratio of $\geq 1.25$ for the prediction of rapid progression of valvar aortic stenosis ($\geq 0.20$ cm²/y) was 64%, 72%, and 80%, respectively (Figure 2). There were 12

![Figure 2](image-url)
subjects (14%) with an AVA ratio of <1.0 and only 4 subjects with an AVA ratio of <0.9. The baseline AVA in those with a ratio of <0.9 was 1.2±0.3 cm². The initial AVA was larger in patients with rapid progression than in those with slow progression (Table), but no discrete level of initial AVA could be identified that was associated with a higher likelihood of rapid progression. The duration from entry into the study to the most recent echocardiographic follow-up was longer in patients with rapid progression than in those with slow progression (39.1±14.3 versus 28.1±14.9 months, P<0.005). A multivariable analysis found an AVA ratio of ≥1.25 (P=0.006) and follow-up duration (P<0.005), to be independent predictors of rapid progression.

When the change in AVA was analyzed as a continuous variable, the only factors with which it correlated were initial AVA (P=0.02, r=0.28) and follow-up duration (P=0.006, r=0.31). When the AVA ratio was analyzed as a continuous variable against the rate of progression in patients with only mild aortic stenosis (AVA ≥1.20 cm²), there was a difference between rapid and slow progressors (1.32±0.23 versus 1.17±0.14, P=0.05). An AVA ratio of ≥1.25 was predictive of rapid progressors (P=0.007). In patients with mild aortic stenosis, the sensitivity, specificity, and positive predictive value of an AVA ratio of ≥1.25 to predict those destined to progress rapidly was 66%, 82%, and 85%, respectively (Figure 3).

Reproducibility of Measurements
The interobserver and intraobserver variabilities in the measurement of the AVA ratio are 0.01±0.01 and 0.03±0.04, respectively.

Discussion
The results of the present study illustrate that aortic stenosis is a progressive disease and that there is substantial individual variability in the rate of progression (Figure 4). We showed that throughout the ejection phase of the cardiac cycle, the AVA does not remain constant and that in patients with aortic stenosis, the rate of change in AVA as expressed by the AVA ratio is a reliable predictor of an individual’s risk of rapid versus slow hemodynamic progression. Our results indicate that the discriminative power of the AVA ratio (mid-deceleration [Md]/mid-acceleration [Ma]) is such that it may be used to help risk stratify patients with stenotic aortic valve disease and therefore is clinical information to be incorporated into a decision-making algorithm. An individual with an AVA of ≥0.9 cm² and a large AVA ratio is likely to be a rapid progressor. If, however, the AVA ratio is not increased, conclusions cannot be made with respect to the risk of rapid hemodynamic progression (Figures 2 and 3).

Rapid progressors had an initial AVA that was slightly larger than that of the slow progressors. We suggest that those with a larger valve area have proportionally more valve area to lose, thus showing a greater magnitude of progression.

AVA Ratio
The AVA ratio is a ratio of AVA, as measured with the continuity equation that is calculated at 2 separate time points during ejection. In the present study, the 2 time points chosen were those at Ma (1/2a) and at Md (1/2d). Although any number of time points could have been chosen, we chose 1/2a and 1/2d because these were the time points used in previous studies that described aortic valve dynamics measured with

![Figure 3](http://circ.ahajournals.org/content/101/14/1950/F3.large.jpg)

**Figure 3.** Top, in patients with baseline AVE ≥1.2 cm², number of rapid and slow progressors for AVA ratio <1.25 and ≥1.25. Bottom, in patients with baseline AVA ≥1.2 cm², receiver operating characteristic curve for AVA ratio. AUC indicates area under the curve.

![Figure 4](http://circ.ahajournals.org/content/101/14/1950/F4.large.jpg)

**Figure 4.** Plot of annual rate of progression for each patient. Note substantial individual variability. Each point represents 1 patient.
Doppler echocardiography. The AVA ratio was defined as 
AVA (1/2a)/AVA (1/2d). The rate of change in AVA during 
ejection will directly affect the AVA ratio. A valve, which 
opens and closes slowly, will have a smaller value for AVA 
(1/2a) and a larger value for AVA (1/2d) compared with the 
AVA measured at peak velocity, which will therefore have a 
larger AVA ratio. An explanation for why the AVA is largest 
at Md when flow velocity has decreased was proposed by 
Badano et al, who suggested that the kinetic energy required 
to initiate motion in calcified and stiff valves is significantly 
more than that required to further move the valve once it is in 
motion. In addition, given a constant flow, the flow velocity 
through a smaller orifice may be greater than that through a 
larger orifice.

**Relationship Between AVA Ratio and Aortic 
Stenosis Progression**

Aortic stenosis progression is usually defined as the rate at 
which AVA, measured at a single point in the cardiac cycle, 
decreases over time. A measure of AVA at only one time 
point during ejection cannot be used to comprehensively 
evaluate the true severity of stenotic aortic valve disease. A 
previous study of valve dynamics in patients with aortic 
stenosis found no relationship between the magnitude of 
change in effective AVA measured during ejection and the 
usual indices of aortic stenosis severity, such as AVA 
measured at peak transaortic flow velocity. Our results 
indicate that a more detailed evaluation of AVA can provide 
additional insight into the severity of aortic stenosis.

Regardless of the AVA measured at peak transaortic flow 
velocity, valves with a slower rate of change in area during 
ejection suggest the presence of more significant disease. We 
confirmed our hypothesis that in patients with an AVA of 
≥0.9 cm², a larger AVA ratio would be a marker of more 
severe aortic stenosis and thus that those with a large AVA 
ratio (Md/Ma ≥1.25) are more likely to progress rapidly. 
However, as the aortic valve leaflets continue to thicken and 
calciﬁy, they may eventually become completely immobile 
and therefore have a zero rate of change in area. We expected 
the relationship between the AVA ratio and the rate of 
progression to be nonlinear, so we decided a priori to exclude 
patients with more severe aortic stenosis (AVA <0.9 cm²). 
Despite this cutoff point, we could not use the AVA ratio 
analyzed as a continuous variable to identify patients destined 
for rapid progression of aortic stenosis. However, when 
patients with only mild aortic stenosis (AVA ≥1.2 cm²) were 
evaluated, the AVA ratio as a continuous predictor variable 
became a signiﬁcant predictor of risk of rapid progression 
and the discriminative power of the test was stronger (greater 
sensitivity, specificity, and positive predictive power).

**Rate of Change in AVA Over Time**

As the AVA decreases, the propensity for rapid hemodynamic-
progression increases. The results of the present study also 
showed that the duration of patient follow-up was longer in 
those who were rapid progressors. This reﬂects the fact that 
the rate of change in AVA over time is not linear and that the 
longer a patient is followed, the more likely that the steep 
portion of the curve will be reached (Figure 5). In patients 
with mild or mild to moderate aortic stenosis, the AVA ratio 
may help to locate an individual’s position on the flat portion 
of the curve (Figure 5).

**Study Limitations**

The present study was subject to several important limitations. 
Because Doppler tracings could not be acquired simulta-
nously, it is possible that subtle hemodynamic changes 
occurred between the recording of the left ventricular outflow 
tract flow velocity (V₁,0VT) and aortic flow velocity (V₀AO). In 
an attempt to minimize this limitation, Doppler tracings were 
matched for ejection time. The rate of change in orifice area 
will be inﬂuenced by left ventricular systolic function. In 
patients with an AVA ratio of ≥1.25, the baseline ejection 
fraction was slightly lower than that in patients with a smaller 
ratio. However, a reduction in left ventricular systolic perfor-
ance should result in a reduction in the AVA ratio, which 
would only weaken what proved to be robust results. In 
addition, the mean ejection fraction was still within the 
normal range (61%) in those with an AVA ratio of >1.25.

A complete spectral Doppler envelope is required to 
accurately determine the AVA ratio. We were able to deter-
mine the AVA ratio in 74% of the study subjects. The use of 
left-sided contrast agents has been shown to enhance the 
sensitivity of spectral Doppler. When the enhancement of 
the Doppler signal with an ultrasound contrast agent was 
evaluated in 51 patients with aortic stenosis, the Doppler envelope 
was enhanced for all jets and the hemodynamic correlation 
with invasive pressure measurements was improved. The 
combination of improved spectral Doppler sensitivity with 
the new echocardiographic equipment, the commercial avail-
ability of left-sided contrast agents, and the care taken by 
sonographers when obtaining the Doppler envelope will 
greatly enhance the universal applicability of this method.

It is conceivable and probable that the variables in the 
Bernoulli equation differ at different times of ejection. 
However, this should not affect the results of our study. The 
total effect on flow dynamics was evaluated, and because 
the same time points during ejection were measured in each 
subject, the effects on flow determined with the Bernoulli 
equation would be similar among subjects.

The interobserver and intraobserver variabilities in the 
measurement of the AVA ratio were small. Because all 
measurements were made from representative Doppler trac-
ings that had been captured and digitized from the original 
 videotaped images, this will likely reduce repeated measure
variability. However, multiple continuous- and pulsed-wave Doppler tracings were captured, and the choice of which tracings to measure was left to the discretion of the individual making the measurement. By not ensuring that the same Doppler envelopes were measured, we believe that a representative account of variability could be expressed.

Although the concept of trying to determine instantaneous AVA is not new, the clinical application of this concept is novel. The results of the present study are provocative and enticing to the clinician when the rate of aortic stenosis progression is an important variable in the decision-making algorithm. We believe that the measurements made in this study are feasible for any clinical echocardiographic laboratory, but a validation set is required to confirm the accuracy and veracity of this novel approach.

Clinical and Research Implications

The method used in the present study to evaluate valve dynamics is practical for routine clinical use. This method involves the use of continuous- and pulsed-wave Doppler tracings, which are a standard component of the Doppler evaluation of patients with aortic stenosis. In addition, the time required to calculate the AVA ratio is modest. There are a number of clinical arenas in which this modality of evaluating stenosis severity may be of practical use, as follows.

(1) Patients with aortic stenosis of a lesser severity than would routinely require surgical intervention, for whom cardiac surgery is planned for other reasons, present physicians with a challenging clinical decision. Because the AVA ratio helps in the prediction of an individual’s risk of rapid progression, it may aid the clinician with the decision regarding prophylactic aortic valve replacement. Although promising, the usefulness of the AVA ratio as a predictor of the pending rate of hemodynamic progression deserves further clinical validation. In patients with aortic stenosis and an AVA of <0.9 cm², no inferences about the relationship between the AVA ratio and the rate of hemodynamic progression can be made on the basis of the present study.

(2) A measure of valve dynamics may also provide insight to the puzzling relationship between hemodynamic stenosis severity and clinical symptoms.

(3) Because effective orifice area is flow dependent, when the transaortic flow is low, aortic stenosis may be misdiagnosed. A small AVA in association with a low transvalvular gradient should raise the suspicion that the reduced aortic orifice area may be “flow dependent.” To better evaluate this, the recent American College of Cardiology/American Heart Association guidelines on the management of valvular heart disease suggest that it may be useful to determine valve area and pressure gradient after a dobutamine infusion. If the concern is to exclude flow-dependent aortic stenosis, then the analysis of AVA during the ejection phase of a cardiac cycle may preclude the need for pharmacological interventions. Preliminary data suggest that this is a reasonable concept.

References

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