Nomograms for severity of aortic valve stenosis using peak aortic valve pressure gradient and left ventricular ejection fraction

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Aims Continuity equation to evaluate aortic valve area (AVAEC) is critically dependent on accurate measurement of left ventricular outflow tract diameter and velocity. To circumvent these limitations, the present study aimed to generate nomograms for a facilitated estimation of aortic valve area using peak aortic valve pressure gradient (ΔpAv) and left ventricular ejection fraction (LVEF).

Methods and results Two hundred and fifty-five subjects with non-invasively and invasively defined aortic valve stenosis (AS) formed the basis of this study. Basis of the nomograms was the correlation analysis between ΔpAv and AVA as estimated by AVACE within different LVEF groups. LVEF differed from 65.6 ± 1.8% (Group I, LVEF > 60%) to 34.5 ± 4.3% (Group IV, LVEF ≤ 30%). ΔpAv and AVA varied from 85.6 ± 19.5 mmHg and 0.69 ± 0.16 cm² in Group I to 58.5 ± 15.9 mmHg and 0.73 ± 0.23 cm² in Group IV (ΔpAv: P < 0.001). Mean AVACE showed no significant difference between the groups. Correlation between ΔpAv and AVACE was statistically significant with P < 0.001 in all subgroups (R² between 0.72 and 0.76). Furthermore, a prospective estimation of AVA using the developed nomograms correlated very well with invasively determined AS using the Gorlin formula (R² = 0.76, SEE = 0.21 cm², bias 0.04 cm²).

Conclusion The present study has established and confirmed a solid, easy to use nomogram-based method to accurately quantify severe AS.

KEYWORDS Aortic valve stenosis; Continuity equation; Nomogram

Introduction Aortic valve stenosis (AS) belongs to the most common cardiac valve lesions.1 Doppler echocardiography is recommended for the diagnosis and assessment of the severity of AS.2–5 However, accurate quantification of the haemodynamic severity of AS from clinical and echocardiographic findings is frequently difficult, particularly in the patient with an impaired echocardiographic window.6–8 Determination of the aortic valve area (AVA) using the continuity equation (AVAEC) from two-dimensional and Doppler echocardiography has gained widespread acceptance. AVA measurement by continuity equation has been validated against and compares favourably to the Gorlin method derived from haemodynamic parameters measured at the time of cardiac catheterization.3,4 Despite the frequent use of AVACE to estimate AS, this method has its limitations. First, it is critically dependent on the accurate measurement of the left ventricular outflow tract (LVOT) diameter. Furthermore, as the measurement of LVOT diameter is squared in the AVACE, a measurement error is magnified. Secondly, the LVOT velocity should be measured exactly at the point where the diameter is determined. These two conditions cannot always be obtained as, often, the anchoring points for measurement are unreliable because of distorted anatomy, poor image resolution, suboptimal technical skill of the echocardiographer, and variability in measurement method and interpretation.7,8 The aim of the present study was to generate nomograms for a reliable estimation of AS severity using two parameters easy to determine at the time of a routine echocardiographic examination: peak aortic valve pressure gradient (ΔpAv) and left ventricular ejection fraction (LVEF). Peak aortic valve velocity, and consequently ΔpAv, was considered the most reliable indicator of AS severity as, compared with LVOT diameter and...
LVOT velocity, the peak velocity of flow through aortic valve is least subject to error. As a means of simplification, the LVEF was estimated subjectively.\textsuperscript{9–12}

**Methods**

**Study population**

The study was conducted at the Department of Cardiology, Heart Center, University of Technology, Dresden, Germany. Potential subjects were identified by searching the echocardiography database for all cases coded as AS between January 2004 and December 2007. This included patients with an anatomically abnormal appearance of the valve and a peak aortic valve velocity >220 cm/s. Exclusion criteria were patients with mitral or aortic regurgitation more than mild according to the ACC/AHA practice guidelines.\textsuperscript{13} Furthermore, only patients with an invasive haemodynamic evaluation of the AS within 2 weeks around echocardiography were included. If a difference of ≥0.2 cm\(^2\) in AWA calculation between echocardiographic (AWACE) and invasive measurement using the Gorlin formula (AWAGF) was obvious, the patient was excluded from nomogram development.\textsuperscript{14} A final cohort of 255 subjects formed the basis of this study. To validate the developed nomograms, an additional study population of 40 patients was analysed prospectively. Hereby, the determined AAVA by use of the nomograms (AVANO) was compared with invasive AVACE measurement.

**Transthoracic echocardiography**

A complete two-dimensional, pulsed-wave, continuous-wave, and colour Doppler echocardiographic examination was performed by experienced investigators using an IE33 echocardiography System (Philips, NL). Subjects were examined in supine, left lateral position. AWACE was calculated with use of the simplified continuity equation, where AWACE = 0.785 \times (Q_{LVOT})\(^2\) \times V_{LVOT}/V_{max}\(^5\) Q_{LVOT} is the diameter of the LVOT (cm) and V_{LVOT} is the velocity measured at the LVOT (m/s) by use of pulsed-wave Doppler. V_{max} is the peak aortic valve velocity (m/s) assessed with continuous-wave Doppler from the window that gave the highest velocity signal. \(\Delta p_{Av}\) was calculated using the modified Bernoulli equation \((\Delta p_{Av} = 4 \times V_{max})\). LVEF was estimated by subjective visual analysis.

**Cardiac catheterization**

All patients in the final cohort had cardiac catheterization with a haemodynamic AS evaluation (inclusion criterion). LV and ascending aortic pressures were recorded using fluid-filled catheters (5 or 6Fr) by pull-back technique from the left ventricle to the ascending aorta. The pressure gradient was calculated by superimposing the pressure recordings. Peak-to-peak and mean transvalvular gradients were determined and AWACE was calculated using the Gorlin formula.\textsuperscript{14} \(\Delta p_{Av}\) was calculated with use of the simplified continuity equation, where \(\Delta p_{Av} = \text{CO}/\text{SEP}/(44.3 \times \sqrt{\Delta P})\) where CO is the cardiac output (mL/min), SEP the systolic ejection period, and \(\Delta P\) the transaortic pressure gradient (mmHg). Cardiac output was determined by the Fick method. Severity of AS was classified as mild (AVA ≥1.5 cm\(^2\)), moderate (AVA <1.5 and ≥1.0 cm\(^2\)), and severe (AVA <1.0 cm\(^2\)) according to the ACC/AHA practice guidelines.\textsuperscript{13} Coronary angiography was performed in all patients.

**Statistical analysis**

Demographic data and results are provided as mean values ± SD. The correlation between AWACE and \(\Delta p_{Av}\) was determined by linear regression analysis, including standard errors of the estimate (SEE). Agreement between measurements was evaluated by the standard paired t-test. Furthermore, the Bland-Altman analysis was used to determine the mean of the difference with 95% limits of agreement (±1.95 SD) in a prospective cohort. A two-tailed probability value <0.05 was considered statistically significant.

**Results**

Two hundred and fifty-five subjects with non-invasively and invasively defined AS formed the basis of this study. The mean age of the total study population was 71.2 ± 13 years. Patient data were divided into four groups according to the estimated LVEF: Group I, LVEF > 60%; Group II, LVEF > 50%; Group III, LVEF > 40%; and Group IV, LVEF ≥ 30%. Table 1 shows the characteristics of the patients.

Coronary angiography showed significant stenosis (luminal narrowing ≥50% of the diameter of ≥1 coronary artery) in 105 patients (41%). LVEF differed from 65.6 ± 1.8% in Group I to 34.5 ± 4.3% in Group IV. \(\Delta p_{Av}\) and AWACE differed from 85.6 ± 19.5 mmHg and 0.69 ± 0.16 cm\(^2\) in Group I to 58.5 ± 15.9 mmHg and 0.73 ± 0.23 cm\(^2\) in Group IV (\(\Delta p_{Av}\): \(P < 0.001\), \(\Delta p_{Av}\) and AWACE were 72.8 ± 21.1 mmHg and 0.76 ± 0.23 cm\(^2\) in Group II, respectively, 68.4 ± 15.4 mmHg and 0.72 ± 2.1 mm\(^2\) in Group III. Mean AWACE showed no significant difference between the groups (Figure 1).

For each LVEF group, a diagram was plotted with \(\Delta p_{Av}\) as y-value and AWACE as x-value. Every dot in the diagram represents an individual patient with a data pair consisting of \(\Delta p_{Av}\) and AWACE. Correlation analysis between \(\Delta p_{Av}\) and AWACE was performed in each LVEF group (Figure 2). Correlation coefficients (\(R^2\)) ranged between 0.72 and 0.76. In all LVEF subgroups, the correlation (two tails) between \(\Delta p_{Av}\) and AWACE was statistically significant with \(P < 0.001\).

**How to use the nomograms**

To apply these newly developed clinically easy to use nomograms for AWA estimation, only LVEF and \(\Delta p_{Av}\) need to be determined. First, LVEF (%) has to be defined and appropriate nomogram line chosen. Secondly, \(\Delta p_{Av}\) (mmHg) should be determined by standard continuous-wave Doppler echocardiography as usual. To determine AWA, the intersection between the nomogram line and \(\Delta p_{Av}\) (y-axis) has to be

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**Table 1 Patients characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.2 ± 13</td>
</tr>
<tr>
<td>Female (%)</td>
<td>44</td>
</tr>
<tr>
<td>AWA (cm(^2))</td>
<td>0.73 ± 0.21</td>
</tr>
<tr>
<td>(\Delta p_{Av}) (mmHg)</td>
<td>75.4 ± 21.4</td>
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<tr>
<td>LVEF (%)</td>
<td>56.3 ± 10.5</td>
</tr>
<tr>
<td>Patients with LVEF &gt; 60% (n)</td>
<td>88</td>
</tr>
<tr>
<td>AWA (cm(^2))</td>
<td>0.69 ± 0.16</td>
</tr>
<tr>
<td>(\Delta p_{Av}) (mmHg)</td>
<td>85.6 ± 19.5</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>65.6 ± 1.8</td>
</tr>
<tr>
<td>Patients with LVEF &gt; 50% (n)</td>
<td>93</td>
</tr>
<tr>
<td>AWA (cm(^2))</td>
<td>0.76 ± 0.23</td>
</tr>
<tr>
<td>(\Delta p_{Av}) (mmHg)</td>
<td>72.8 ± 21.1</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>57.9 ± 2</td>
</tr>
<tr>
<td>Patients with LVEF &gt; 40% (n)</td>
<td>42</td>
</tr>
<tr>
<td>AWA (cm(^2))</td>
<td>0.72 ± 2.1</td>
</tr>
<tr>
<td>(\Delta p_{Av}) (mmHg)</td>
<td>68.4 ± 15.4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>46.8 ± 2.5</td>
</tr>
<tr>
<td>Patients with LVEF ≥ 30% (n)</td>
<td>32</td>
</tr>
<tr>
<td>AWA (cm(^2))</td>
<td>0.73 ± 0.23</td>
</tr>
<tr>
<td>(\Delta p_{Av}) (mmHg)</td>
<td>58.5 ± 15.9</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>34.5 ± 4.3</td>
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</table>
identified. By extrapolation of the intersection to the x-axis, AVANO can be read off (Figure 3).

Derived from those nomogram lines, calculation formulas were determined and can be used alternatively to calculate AVANO:

LVEF > 60%: $AVANO = \frac{-(\Delta pAv - 155)}{100.8}$;
LVEF > 50%: $AVANO = \frac{-(\Delta pAv - 133.3)}{79.2}$;
LVEF > 40%: $AVANO = \frac{-(\Delta pAv - 114.4)}{64.2}$;
LVEF > 30%: $AVANO = \frac{-(\Delta pAv - 100.4)}{57.8}$.

Estimation of AVANO using the developed nomograms correlated very well with the invasive estimation of AS in a prospective patient population. Forty patients with AS were used to validate the nomograms by assessing its accuracy at achieving AVANO compared with AVA estimated by the

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Figure 1  Boxplot analysis of (A) AVACE and (B) ∆pAv in different left ventricular ejection fraction groups.

Figure 2  Correlation analysis between AVACE and ∆pAv in different left ventricular ejection fraction groups.
Gorlin formula. For evaluation of precision, patients were grouped based on the estimated L VEF. AVANO was determined using the nomogram as demonstrated above. Hereafter, AVAGF was analysed during invasive measurement. Overall, in 35 patients (88%), the estimated AVANO differed by ±0.1 cm² from AVAGF. The remaining five patients were within a range of ±0.2 cm². The Bland–Altman plot of mean and difference of AVANO and AVAGF showed an excellent agreement between the two methods ($R^2 = 0.76$, SEE = 0.21 cm²). No significant under- or overestimation was obvious with the use of the nomograms (bias 0.04 cm², limits of agreement −0.45, 0.47). The level of agreement between AVANO and AVAGF measurements was additionally evaluated by intraclass correlation (ICC) analysis. The calculated ICC coefficient (0.84) and analysis of variance (0.15) suggest that there is no significant difference between AVANO and AVAGF measurement and the level of concordance between the invasive and the newly described AVA quantification technique is high.

Discussion

The major finding of the present study is that an easy to use and reliable echocardiographic method to accurately estimate AVA in severe stenosis was developed. Basis of the nomograms was the correlation analysis between $DpAv$ and $AVACE$ within different LVEF groups. Patients with a difference of >0.2 cm² between echocardiographic calculated $AVACE$ and invasive $AVAGF$ measurement were excluded from nomogram development. Because of mathematical coupling between $DpAv$ and $AVACE$, a good correlation was expected. This correlation remained stable in patients with varying degrees of AS and LVEF. The continuity equation method for calculating AVA has been validated in comparison to cardiac catheterization (as gold standard) in many studies with excellent results. Notwithstanding, the continuity equation is potentially time-consuming and limited by inaccuracies and inconsistencies in the estimation of some of the variables. First, the measurement of LVOT diameter is subject to the most variability and any errors are magnified (squared) in the formula. Calcification of the aortic valve and poor echocardiographic windows are the major factors that make the measurement of LVOT diameter difficult or almost impossible in some patients. Secondly, the flow velocity in LVOT recorded by pulsed-Doppler may show a skewed velocity distribution with the highest velocities along the anterior wall and septum. Furthermore, this velocity is optimally measured at the same site as the LVOT diameter. Often, however, this assumption is violated as they are measured from different echocardiographic windows. The most reliable parameter is $DpAv$, which also is subject to less methodological caveats. However, it is not sufficient as a stand-alone measure of AS severity as the velocity tends to decrease in the setting of poor left ventricular function. As such, it requires a correction for the function of the left ventricle. A comparable approach has been used by other investigators. An index of fractional shortening divided by peak transaortic pressure gradient was validated in comparison to AVA determined by the Gorlin formula at cardiac catheterization. However, fractional shortening has significant shortcomings in the assessment of left ventricular function in the presence of regional wall motion or conduction abnormalities. Rather than attempting to estimate the EF by fractional shortening, the present method bases on nomogram lines or formulas for different visually estimated LVEF groups. Previous

Figure 3 Nomogram lines showing an exemplary patient with a left ventricular ejection fraction of 35% and a $DpAv$ of 55 mmHg. The nomogram gave an AVANO of ~0.8 cm².
studies have shown that assessing EF visually is accurate in experienced hands. Present data do not imply that patients should be considered for valve replacement based on these nomograms as the decision making process is obviously more complex. Instead, the established method can be used as a screening tool for patients with AS who may require closer follow-up. It may be of particular use when the LVOT diameter or VLVOT cannot be measured reliably.

The described method—as its limitation—is not suitable for accurate quantification of an AVA >1.2 cm² because these patients had no invasive estimation of their AVA and could thereby not included in nomogram development. Extrapolation of the nomogram lines to quantify larger AVAs may be possible, but is hypothetical. Nevertheless, from a clinical standpoint identification of severe AS with AVA <1.0 cm² and an AVA near this margin is essential and validly possible by the method presented. On the other hand, severe AS can be ruled out if \( \Delta pA v \) measurement is clearly below the LVEF-adjusted nomogram line at 1.0 cm² on x-axis. The initial limitation of this study with its mainly retrospective nature was compensated by a prospective validation of the nomograms in 40 patients. This revealed an excellent predictive value of AVA. As patients with moderate or higher mitral or aortic regurgitation were excluded, it is not known how this method will be reliable in that group. In mitral regurgitation, EF may not accurately reflect left ventricular contractility; in aortic regurgitation, \( \Delta pA v \) will reflect not only the degree of aortic stenosis but also the increased flow across the LVOT because of the regurgitant fraction. However, this caveat also weakens other echocardiographic methods for the determination of AVA.

**Conclusion**

The present study establishes a new, easy to use echocardiographic and nomogram-based method to accurately estimate severe AS. It can be used as a screening test or in lieu of the continuity equation particularly when there is problematic estimation of either VLVOT or DLVOT.

**Conflict of interest:** none declared.

**References**