Comparison of Invasive and Noninvasive Assessment of Aortic Stenosis Severity in the Elderly

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Background—Aortic valve area (AVA) in aortic stenosis (AS) can be assessed noninvasively or invasively, typically with similar results. These techniques have not been validated in elderly patients, where common assumptions make them most prone to error. Accurate assessment of AVA is crucial to determine which patients are appropriate candidates for aortic valve replacement.

Methods and Results—Fifty elderly patients (mean 86 years, 46% female) referred for cardiac catheterization to evaluate AS also underwent transthoracic echocardiography within 24 hours. To minimize assumptions all patients had 3-dimensional echocardiography (Echo-3D), and at catheterization using directly measured oxygen consumption (Cath-mVo2) and thermodilution cardiac output (Cath-TD). Correlation between Cath-mVo2 and Echo-3D AVA was poor (r=0.41). Cath-TD AVA had a moderate correlation with Echo-3D AVA (r=0.59) Cath-mVo2 (AVA=0.69 cm²) and Cath-TD (AVA=0.66 cm²) underestimated AVA compared with Echo-3D (AVA=0.76 cm² P=0.08 for comparison with Cath-mVo2; r=0.001 for Cath-TD). Compared with Echo-3D, the sensitivity and specificity for determining critical disease (AVA <0.8 cm²) were 81% and 42% for Cath-mVo2, and 97% and 53% for Cath-TD. The only independent predictor of the difference between noninvasive and invasive AVA was stroke volume index (P<0.01). Resistance, a less flow-dependent measure, showed a stronger correlation between Echo-3D and Cath-mVo2 (r=0.69), and Echo-3D and Cath-TD (r=0.77).

Conclusions—Standard techniques of AVA assessment for AS show poor correlation in elderly patients, with frequent misclassification of critical AS. Less flow-dependent measures, such as resistance, should be considered to ensure that only appropriate patients are treated with aortic valve replacement. (Circ Cardiovasc Interv. 2012;5:00-00.)

Key Words: aortic stenosis ▪ aortic valve area ▪ aortic valve replacement ▪ elderly

Aortic valve replacement (AVR) is the preferred treatment option for octogenarians and nonagenarians with aortic stenosis (AS).1-3 With the advent of transcatheter AVR, even patients who were previously deemed too old or too high risk for surgery may now also be candidates for valve replacement.4 An accurate method of measuring AS severity is crucial to ensure that only appropriate patients are referred for treatment. The typical methods of estimating aortic valve area (AVA) have not been validated in patients 80 years and older, and there is reason to suspect their accuracy in this cohort.5

Echocardiographic estimation of AVA can be performed with the continuity equation,6,7 which typically correlates well with assessment by cardiac catheterization.8-11 Errors with the continuity equation may arise from its assumption of a circular left ventricular outflow tract (LVOT),12 particularly in elderly patients. The Gorlin equation is the standard method for assessing AVA in the cardiac catheterization laboratory.13 Its potential errors include the estimation of cardiac output and the assumptions involved in the Gorlin constant.14 Both invasive assessment with the Gorlin formula and noninvasive assessment with the continuity equation appear to be flow dependent, and correlate most poorly in low flow states.5,15

Elderly patients with AS, especially those who are not surgical candidates, may have comorbidities such as left ventricular dysfunction, ischemic heart disease, or chronic lung disease. Their symptoms should therefore not automatically be attributed to AS. Both surgical and transcatheter AVR involve significant risk as well as cost, and should only be offered to patients with truly critical AS who are expected to benefit from AVR. We hypothesized that standard methods of assessing AS severity would correlate poorly in elderly patients, and performed this study to determine the best means of evaluating AS severity in an elderly patient cohort. Specifically, we had 4 aims: (1) evaluate the error introduced
in noninvasive AS assessment by using 2-dimensional echocardiography, (2) evaluate the error introduced in invasive AS assessment by using various techniques of cardiac output estimation, (3) evaluate the correlation between ideal noninvasive and invasive AS assessment and determine the cause of any poor correlation, and (4) determine whether an alternative measure of AS severity other than AVA would correlate better between noninvasive and invasive assessment.

WHAT IS KNOWN

- Aortic stenosis severity usually is assessed by the aortic valve area, which may be determined noninvasively using echocardiography or invasively using cardiac catheterization.
- Both noninvasive and invasive assessments of aortic valve area may be impacted by assumptions inherent in both techniques, including the shape of the left ventricular outflow tract and estimation of oxygen consumption, and vary based on the cardiac output.

WHAT THE STUDY ADDS

- This article demonstrates the degree to which noninvasive and invasive assessments of aortic valve area agree, and the factors that explain the discrepancies between the two.
- This article demonstrates that when comparing noninvasive and invasive assessments of aortic stenosis of severity, lower cut offs for critical disease should be used for invasive measurement of aortic valve area.
- In the setting of low flow, other measures of aortic stenosis severity, such as resistance, should be used.

Methods

All patients age 80 years and older referred for cardiac catheterization between December 2010, and July 2011, to evaluate AS of at least moderate severity were considered for enrollment. Patients were excluded if they had a bicuspid aortic valve, moderate or greater aortic regurgitation, prior aortic or mitral valve surgery, were hemodynamically unstable, or required supplemental oxygen (excluding direct measurement of oxygen consumption). The protocol was approved by the institutional review board at the University of Pennsylvania, and all patients provided written informed consent.

Echocardiography

Standard Doppler and 2-dimensional transthoracic echocardiograms (Echo-2D) were obtained using Philips IE33 machines (Philips Medical Systems). Left ventricular dimensions were measured from the parasternal long axis view in 2D in standard fashion. LVOT dimension was measured in 2D in the parasternal long axis view in midsystole, and 2D LVOT area was calculated using the assumption of a circular LVOT. Peak and mean aortic valve gradients were measured using continuous wave Doppler (including use of a Pedoff nonimaging continuous wave probe) from standard echocardiographic views. In addition, LVOT and aortic valve velocity time integrals (VTIs) were measured in all patients. For those in atrial fibrillation, an average of 5 cycles was used.

Three-dimensional (Echo-3D) full volume sectors of the LVOT were acquired from the parasternal long axis view using a Philips X3-1 real time 3D transthoracic probe (Philips Medical Systems). The full volume sectors then were cropped and analyzed offline using QLAB software (Philips Medical Systems). The full volume sectors were reconstructed in orthogonal planes to obtain a true short axis, and the maximal area of the LVOT in midsystole was measured via direct planimetry 0.5 cm below the aortic leaflets.

Cardiac Catheterization

All patients underwent standard right and left heart catheterization via a femoral approach. Small doses of conscious sedation were used as necessary for patient comfort. Aortic valve gradients were measured using a fluid-filled, dual-lumen pigtail catheter with simultaneous measurement from the left ventricle and proximal ascending aorta. Equal pressures from both lumens were confirmed in the ascending aorta. For patients in atrial fibrillation, an average of 5 cycles was used. All hemodynamic measurements were collected within 3 minutes of valve gradient assessment. For calculating Fick cardiac output, systemic arterial and pulmonary arterial oxygen saturation and hemoglobin were measured from at least 2 samples. After measuring saturations, cardiac output was measured by thermodilution performed using 10 mL boluses of room temperature saline. Five samples were obtained, the highest and lowest were discarded, and the remaining samples were averaged.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>86 (range 80–96)</td>
</tr>
<tr>
<td>Female</td>
<td>46% (n=23)</td>
</tr>
<tr>
<td>White</td>
<td>90% (n=45)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>88% (n=44)</td>
</tr>
<tr>
<td>Angina</td>
<td>32% (n=16)</td>
</tr>
<tr>
<td>Syncope</td>
<td>18% (n=9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>76% (n=38)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>22% (n=11)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>78% (n=39)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>2% (n=1)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>66% (n=33)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>22% (n=11)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>42% (n=21)</td>
</tr>
</tbody>
</table>

Figure 1. Bland-Altman analysis comparing 2-dimensional and 3-dimensional echocardiographic assessment of aortic valve area. Inner dashed line is the mean difference. Outer dashed lines are 0.2 cm² references.
Oxygen consumption (VO₂) was directly measured using an Ultima CardiO₂ breathing analyzer (Medgraphics). All patients were tested for 5 minutes prior to valve assessment to assure comfort and stable breathing. Oxygen consumption then was measured continuously for 3 minutes while aortic valve gradients were assessed and other measurements were performed, with the mean VO₂ over that time period used for analysis.

### Hemodynamic and Aortic Valve Area Assessments

Stroke volume was calculated noninvasively as the area of the LVOT divided by systolic ejection time. Aortic valve area was calculated as noninvasive systolic blood pressure plus the mean gradient divided by transvalvular flow rate. Transvalvular flow was calculated as the stroke volume multiplied by heart rate. Transvalvular flow rate was calculated as the stroke volume divided by systolic ejection time. Aortic valve area was calculated using the continuity equation as stroke volume divided by aortic valve VTI. Resistance was calculated as the mean valve gradient divided by transvalvular flow rate. Valvulo-arterial impedance was calculated as noninvasive systolic blood pressure plus the mean transvalvular gradient divided by the stroke volume indexed for body surface area (BSA).

Cardiac outputs derived from cardiac catheterization were measured using the thermodilution technique (Cath-TD), catheterization using an estimated VO₂ using the LaFarge formula (Cath-LaFarge), and catheterization using measured VO₂ (Cath-mVO₂).

### Statistical Analysis

Continuous variables were compared with a t test, using a paired samples technique where appropriate. Measures of AVA, resistance, and valvulo-arterial impedance were compared using the Bland-Altman method, as well as with bivariate linear regression and Pearson correlation. We also show the percentage of measures of AVA that fall within 0.2 cm² for each technique that was compared. We also compared the techniques’ correlation by AS severity classification, using a valve area <0.8 cm² as critical, ≥0.8 cm² to <1.0 cm² as severe, ≥1.0 cm² to <1.5 cm² as moderate, and ≥1.5 cm² as mild. Correlation by class was tested using Goodman and Kruskal gamma. For determining sensitivity and specificity within invasive techniques, Cath-mVO₂ was used as a reference standard, while Echo-3D was used as a reference standard for noninvasive assessment. For comparisons between noninvasive and invasive assessment, we focused on Cath-mVO₂ and Cath-TD as compared with Echo-3D, the techniques that used the fewest assumptions. We constructed receiver operating characteristic curves to determine the ability of the invasive techniques to determine critical AS as determined by Echo-3D. We examined the difference between invasive and noninvasive assessment within several prespecified subgroups (stroke volume index, BSA, hypertension, atrial fibrillation, gender, and the difference between invasive and noninvasively obtained aortic valve gradients). Low flow was defined as a stroke volume <35 mL/m² by Echo-3D. Those variables with P<0.1 then

### Table 2. Hemodynamic Comparisons Between Invasive and Noninvasive Testing

<table>
<thead>
<tr>
<th>Measure</th>
<th>Echo-2D</th>
<th>Echo-3D</th>
<th>Cath-mVO₂</th>
<th>Cath-TD†</th>
<th>P Value (Cath-mVO₂ vs Echo-3D)</th>
<th>P Value (Cath-TD vs Echo-3D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>72 (±11)</td>
<td>72 (±11)</td>
<td>72 (±13)</td>
<td>72 (±13)</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>137 (±22)</td>
<td>137 (±22)</td>
<td>148 (±29)</td>
<td>148 (±29)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean gradient (mm Hg)</td>
<td>37 (±13)</td>
<td>37 (±13)</td>
<td>44 (±16)</td>
<td>44 (±16)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.73 (±0.19)</td>
<td>0.76 (±0.21)*</td>
<td>0.69 (±0.29)</td>
<td>0.66 (±0.25)</td>
<td>0.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume index (mL/m²)</td>
<td>36.5 (±9.7)</td>
<td>38.2 (±10.4)*</td>
<td>31.7 (±9.5)</td>
<td>30.3 (±8.1)</td>
<td>&lt;0.001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transvalvular flow rate (mL/s)</td>
<td>195 (±40)</td>
<td>205 (±43)*</td>
<td>195 (±66)</td>
<td>185 (±54)</td>
<td>0.27</td>
<td>0.01</td>
</tr>
<tr>
<td>Resistance (dynes*sec/cm⁵)</td>
<td>261 (±103)</td>
<td>248 (±96)*</td>
<td>339 (±167)</td>
<td>349 (±170)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Impedance (mm Hg*㎡/mL)</td>
<td>5.04 (±1.24)</td>
<td>4.81 (±1.16)*</td>
<td>6.51 (±2.17)</td>
<td>6.68 (±1.99)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*P<0.001 for comparison with Echo-2D.
†None of the comparisons between Cath-mVO₂ and Cath-TD were significantly different.

### Table 3. Differences in Aortic Valve Area Calculation

<table>
<thead>
<tr>
<th>AVA Measure</th>
<th>Mean Difference (cm²)</th>
<th>Lower 95% CI of the Mean (cm²)</th>
<th>Upper 95% CI of the Mean (cm²)</th>
<th>P Value</th>
<th>Within 0.2 cm²</th>
<th>Severity Class Agreement</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo-2D–Echo-3D</td>
<td>−0.036</td>
<td>−0.053</td>
<td>−0.019</td>
<td>0.0001</td>
<td>98% (n = 49)</td>
<td>82%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cath-BSA–Cath-mVO₂</td>
<td>0.122</td>
<td>0.088</td>
<td>0.156</td>
<td>&lt;0.0001</td>
<td>70% (n = 35)</td>
<td>74%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cath-Weight–Cath-mVO₂</td>
<td>0.109</td>
<td>0.063</td>
<td>0.154</td>
<td>&lt;0.0001</td>
<td>74% (n = 37)</td>
<td>72%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cath-LaFarge–Cath-mVO₂</td>
<td>−0.112</td>
<td>−0.148</td>
<td>−0.075</td>
<td>&lt;0.0001</td>
<td>82% (n = 41)</td>
<td>76%</td>
<td>0.014</td>
</tr>
<tr>
<td>Cath-TD–Cath-mVO₂</td>
<td>−0.032</td>
<td>−0.078</td>
<td>0.013</td>
<td>0.154</td>
<td>82% (n = 41)</td>
<td>76%</td>
<td>0.001</td>
</tr>
<tr>
<td>Echo-3D–Cath-mVO₂</td>
<td>0.070</td>
<td>−0.010</td>
<td>0.150</td>
<td>0.083</td>
<td>46% (n = 23)</td>
<td>56%</td>
<td>0.055</td>
</tr>
<tr>
<td>Echo-3D–Cath-TD</td>
<td>0.103</td>
<td>0.042</td>
<td>0.164</td>
<td>0.001</td>
<td>58% (n = 29)</td>
<td>70%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

AVA indicates aortic valve area; Echo-2D, 2-dimensional echocardiography; Echo-3D, 3-dimensional echocardiography; Cath-BSA, catheterization using an estimated VO₂ based on body surface area; Cath-mVO₂, catheterization using measured VO₂; Cath-Weight, catheterization using an estimated VO₂ based on weight; Cath-LaFarge, catheterization using an estimated VO₂ using the LaFarge formula; Cath-TD, catheterization using thermodilution.
were included in a multivariate analysis to determine the independent predictors of the difference between invasive and noninvasive assessment. All significance tests were 2-sided, and \( P<0.05 \) was considered significant.

**Results**

Fifty-two patients referred for cardiac catheterization met the study entry criteria. One patient could not tolerate \( \dot{VO}_2 \) testing and 1 patient did not have suitable images for echocardiography. The remaining 50 patients comprise the study cohort. Baseline characteristics of the study population are shown in Table 1. The mean age was 86 years (range 80–96), almost half were female, and most patients presented with dyspnea (88%). The mean left ventricular ejection fraction was 58%. The indication for cardiac catheterization was preprocedure evaluation for transcatheter AVR in 58%, evaluation for open AVR in 24%, and evaluation of progressive cardiac symptoms (dyspnea, angina, or syncope) in the remainder. No patient had an adverse event associated with either invasive or noninvasive testing.

**Echocardiography Findings**

Bland-Altman analysis comparing Echo-2D and Echo-3D AVA is shown in Figure 1. There was a very strong correlation between both measures \( (r=0.956, P<0.0001) \), but AVA estimates were slightly lower using Echo-2D as compared with Echo-3D \( (0.73 \text{ cm}^2 \text{ versus } 0.76 \text{ cm}^2, P=0.0001; \) Tables 2 and 3). Despite nearly all AVA measurements being within 0.2 \( \text{cm}^2 \) of each other, and a strong correlation in classification, there were 16% false-positives where Echo-2D incorrectly classified AS as critical compared with a reference standard of Echo-3D (Table 3 and Figure 2).

**Cardiac Catheterization Findings**

There was a strong correlation between Cath-m\( \dot{VO}_2 \) AVA and the other invasive measures \( (r \text{ values from } 0.842–0.952; \) \( P<0.0001 \) for all). There was not a significant difference between Cath-m\( \dot{VO}_2 \) and Cath-TD AVA \( (0.69 \text{ cm}^2 \text{ versus 0.66 cm}^2, P=0.15) \). However, estimates incorporating assumptions based on body weight and size significantly overestimated AVA. In contrast, the LaFarge equation resulted in AVAs that were significantly smaller than those derived from Cath-m\( \dot{VO}_2 \) (Table 3). Bland-Altman analyses are shown in Figure 3. All of the invasive modalities had similar overall severity classification correlations with Cath-m\( \dot{VO}_2 \) AVA class (Table 3). However, AVA assessments using body size had high percentages of false-negatives for determining critical disease, while using Cath-LaFarge resulted in many false-positives for critical disease. Cath-TD also led to a high percentage of false-positives for critical AS compared with a reference standard of Cath-m\( \dot{VO}_2 \) (Figure 2).

**Comparison Between Invasive and Noninvasive Aortic Valve Area**

Although mean Echo-3D AVA and Cath-m\( \dot{VO}_2 \) AVA were not significantly different, their correlation was poor \( (r=0.412) \). Less than half of the measures were within 0.2 \( \text{cm}^2 \), and only a little more than half were in the same AS severity class, with no significant correlation by gamma test \( (P=0.055; \) Figure 4 and Table 3). Cath-TD AVA had a moderate correlation with Echo-3D AVA \( (r=0.585, P<0.001) \), but was significantly smaller (Figure 5). Using Echo-3D AVA as a reference standard, both invasive methods had a rate of false-positives for the diagnosis of critical AS of about 50% (Figure 2). Cath-TD AVA, however, did have a significant correlation with Echo-3D AVA for AS severity classification \( (P<0.001; \) Table 3). Finally, we also compared the modalities using a less severe cut off for AVA of 1.0 \( \text{cm}^2 \). Using Echo-3D AVA as a reference standard, the sensitivity and specificity of Cath-m\( \dot{VO}_2 \) were 86% and 33%, and for Cath-TD they were 91% and 50%. We constructed ROC curves to determine the potential for invasive measures to assess critical AS as determined by Echo-3D (Figure 6). Thermodilution showed a better correlation (area under the curve \( =0.86 \)) than Cath-m\( \dot{VO}_2 \) (area under the curve \( =0.80 \)). For both invasive measures the ideal cut off for critical AS was an AVA of 0.65 \( \text{cm}^2 \).

By univariate analysis, stroke volume index, BSA, and gender were correlated strongly with the difference between invasive (both Cath-m\( \dot{VO}_2 \) and Cath-TD) and noninvasive AVA \( (P \leq 0.01) \), and the difference in transvalvular gradients also was correlated \( (P<0.1) \). After multivariate analysis, only stroke volume index remained independently predictive of the difference in AVA between methods \( (r= -0.591 \text{ for Cath-m\( \dot{VO}_2 \)}; \) and \( r= -0.568 \text{ for Cath-TD AVA compared with Echo-3D AVA; } P<0.01 \text{ for both}) \). The difference in AVA for Cath-m\( \dot{VO}_2 \) versus Echo-3D as a function of flow (stroke volume index) is shown in Figure 7.

**Resistance and Impedance**

Due to the observed influence of flow (stroke volume index) on the correlation between invasive and noninvasive assessments of AVA, we evaluated 2 other measures of AS severity, resistance and valvulo-arterial impedance which are considered less flow dependent. Both invasive measures of resistance and impedance tended to overestimate the severity of
AS compared with noninvasive assessment (Table 2). There was a moderate correlation between invasively and noninvasively measured resistance ($r_{Cath-mVO2/Echo-3D} = 0.69$, $r_{Cath-TD/Echo-3D} = 0.77$; $P < 0.001$ for both; Figure 8). Stroke volume index had no impact on the difference between invasively and noninvasively measured resistance (for Echo-3D and Cath-mVO$_2$, $r = -0.273$; using Cath-TD $r = -0.271$). Correlation of measurements between invasive and noninvasive impedance was very poor ($r_{Cath-mVO2/Echo-3D} = 0.18$, $P = 0.22$ for Cath-mVO$_2$ and Echo-3D; $r = 0.29$, $P = 0.04$ for Cath-TD and Echo-3D; Figure 9). We also compared transvalvular gradients, stroke volume index, and transval-

Figure 3. Bland-Altman analysis comparing different invasive techniques with catheterization using directly measured oxygen consumption assessment of aortic valve area. Inner dashed line is the mean difference. Outer dashed lines are 0.2 cm$^2$ references. AVA indicates aortic valve area; Echo-2D, 2-dimensional echocardiography; Echo-3D, 3-dimensional echocardiography; Cath-BSA, catheterization using an estimated VO$_2$ based on body surface area; Cath-mVO$_2$, catheterization using measured VO$_2$; Cath-Weight, catheterization using an estimated VO$_2$ based on weight; Cath-LaFarge, catheterization using an estimated VO$_2$ using the LaFarge formula; Cath-TD, catheterization using thermodilution.

Figure 4. Bland-Altman analysis (A) and linear regression (B) comparing Echo-3D and catheterization using directly measured oxygen consumption (Cath-mVO$_2$) assessment of aortic valve area. A, inner dashed line is the mean difference and outer dashed lines are 0.2 cm$^2$ references. AVA indicates aortic valve area.
vular flow rate, essentially all of which were significantly different between the invasive and noninvasive techniques (Table 2).

**Discussion**

We performed invasive and noninvasive assessments of AS severity in an elderly cohort of patients (mean age 86 years) being considered for open or transcatheter AVR to determine the best method of determining which patients should be candidates for therapy. Regarding the 4 goals set forth in the Introduction, we found the following: (1) 2-dimensional echocardiography introduces significant error in AS classification compared with Echo-3D, (2) estimates of cardiac output with different methods may lead to significant error in AS classification using invasive techniques, (3) noninvasive and invasive AS assessments correlate poorly, even when assumptions are minimized, a difference that is driven by stroke volume, and (4) resistance, but not impedence (both of which are less flow dependent measures of AS), provides a better correlation between noninvasive and invasive AS assessments.

**Comparison of Noninvasive Techniques**

Although there was a very strong correlation between measures, we found that 18% of patients had differing classification of AS severity, and 16% of patients without critical AS by Echo-3D were identified by Echo-2D as having critical AS. The strong correlations between Echo-3D and Echo-2D in our study differ as compared with the observations of Gutierrez-Chico et al,18 who showed a more modest correlation between the 2 methods. While we are unaware of any other study that has examined the differences in classification using Echo-3D as the reference method in a similar population, O’Brien et al19 found similar results using computed tomography scanning to determine a 3D LVOT area. Studies in younger patients without AS also have shown that Echo-2D underestimates the LVOT area,12,20 which may explain the tendency of Echo-2D to estimate a smaller AVA than Echo-3D.

**Comparison of Invasive Techniques**

The Fick method for calculating cardiac output requires a value for VO₂, which can be directly measured or calculated using various formulas. Several formulas for estimating VO₂ have been developed.16,17 All have shown variable reliability,21–23 and none have been validated in an elderly cohort. Thermodilution is an alternative method of measuring cardiac output,24 which makes no assumptions for age, but it has proven unreliable at both low outputs25 and at high ones.26,27 We found that the agreement between different measures of invasive AVA was generally strong. However, as compared with Cath-mVO₂, estimates of VO₂ based on body size significantly overestimated AVA, while use of the LaFarge formula significantly underestimated it, resulting in a high rate of misclassification of AS severity.

Practically speaking, these observed differences in AVA measurements relate to overestimation of the cardiac output using body size based methods and underestimation of the cardiac output via the LaFarge method. Our data suggest that there is less of a relationship between body size and cardiac output and, therefore, less potential for error in invasive assessment of AS severity.
output in the elderly, which may explain the tendency to overestimate cardiac output by these methods. The LaFarge formula, which is ideal in children with fast heart rates, would be expected to underestimate cardiac output, and therefore AVA, in the elderly population we studied.17 Thermodilution was not significantly different from measured VO_{2} estimates of AVA, yet its correlation was slightly weaker than the other methods.

Comparison Between Invasive and Noninvasive Techniques

Several studies have shown a strong correlation between invasive and noninvasive AVA assessments in a younger population.8–11 A poorer correlation between the Gorlin and continuity equations has been reported in 1 study of elderly patients.5 We performed Echo-3D and used Cath-mVO\textsubscript{2} and Cath-TD to determine whether the poor correlation between AVAs in our population was due to the assumptions often made when using these formulas or due to the techniques themselves. We found a very poor correlation between Echo-3D and Cath-mVO\textsubscript{2} AVA, while Cath-TD AVA showed a moderate correlation with Echo-3D AVA. Both invasive methods underestimated AVA compared with Echo-3D, similar to the findings of Burwash et al.5 We found that an invasive AVA of 0.65 cm\textsuperscript{2} is best to correlate with critical AS by Echo-3D. This suggests that even in their ideal forms, the continuity and Gorlin equations are not equivalent in elderly patients.

Stroke volume index was the only independent predictor of the difference in AVA between invasive and noninvasive assessments. This is not surprising, as both the continuity and Gorlin equations are known to vary with flow.15 The strong correlation between Cath-TD and Echo-3D AVA in Gutierrez-Chico et al’s18 study likely reflects the higher cardiac outputs in their patients, which were 40% higher than those in our population.

Flow Independent Assessment of Aortic Stenosis Severity

We evaluated 2 other techniques for assessing AS severity that are considered less flow dependent: resistance28 and valvulo-arterial impedance.29 We found that resistance had a good correlation between both invasive measures and noninvasive assessment, stronger in both cases than the correlation between AVAs, and did not vary based on flow. Nevertheless, invasively measured resistance consistently overestimated the severity of AS compared with noninvasive measurement, and impedance showed very poor correlations between invasive and noninvasive techniques, and thus appears less useful in these patients.

Study Limitations

There is no clear gold standard for AVA assessment. Therefore, we can only draw conclusions regarding the correlation between the techniques rather than their absolute accuracy. When considering sensitivity and specificity of invasive and

Figure 7. The difference between 3-dimensional echocardiography (Echo-3D) aortic valve area and catheterization using directly measured oxygen consumption aortic valve area is plotted versus the stroke volume index obtained from Echo-3D. AVA indicates aortic valve area.

Figure 8. Bland-Altman analysis (A) and linear regression (B) comparing Echo-3D and catheterization using directly measured oxygen consumption assessment of aortic valve resistance. A, inner dashed line is the mean difference and outer dashed lines are 2 standard deviations. Echo-3D indicates 3-dimensional echocardiography; Cath-TD, thermodilution cardiac output.
noninvasive techniques, we used echocardiography as the reference standard, because this technique is the most widely used. Limitations of cardiac catheterization include the use of mild conscious sedation, which may depress cardiac output, and the use of a catheter across the aortic valve, which may increase the measured gradient. All invasive assessments were based on the assumption that measured VO2 with the Fick equation is the most accurate, yet even this technique may have the potential for error, depending on the collection method and patient state, and we found that thermodilution correlated better with noninvasive assessment. Limitations of echocardiography in our study also relate to the assessment of gradients. Although we used nonimaging, pressure-only probes whenever possible, the higher values for invasive assessment may reflect a suboptimal axis for assessment in some cases. However, the difference in gradient did not predict the difference between invasive and noninvasive assessments, and likely had minimal impact. In addition, these are real world limitations of the techniques currently used for AS evaluation.

Clinical Implications
Current guidelines suggest that invasive assessment of AS severity should be undertaken when there is discrepancy between clinical symptoms and noninvasive findings, a situation that might easily arise in elderly patients with left ventricular diastolic dysfunction, low stroke volume, and other comorbidities, where clearly linking symptoms to aortic valve disease may be difficult. However, there is no evidence that invasive assessment will more reliably determine the severity of AS in this situation, due to the limitations of standard techniques, and in fact may only introduce further confusion, as our study showed. Based on our findings we recommend that clinicians use 3D echocardiography for noninvasive AS evaluation, and thermodilution measures of cardiac output when invasive assessment is undertaken. A lower value of AVA, such as 0.65 cm², may be required to determine critical AS invasively. Furthermore, because the discrepancies between methods vary based on stroke volume, application of less flow-dependent measures, such as aortic valve resistance, also should be considered.

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Disclosures
None.

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