Original articles

Reliability of new and old Doppler echocardiographic indexes of the severity of aortic stenosis in patients with a low cardiac output

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Aortic stenosis; Echocardiography; Left ventricular insufficiency.

Background. **In addition to the conventional "flow-corrected" parameters (continuity equation and aortic valve resistance), new and simpler Doppler echocardiographic indexes of the severity of aortic stenosis have recently been introduced. These measures can be classified as "function-corrected" indexes (fractional shortening-velocity ratio and ejection fraction-velocity ratio) and "pressure-corrected" indexes (percent stroke work loss). Little information however is available about the diagnostic accuracy of each of these parameters in identifying patients with severe aortic stenosis in low-flow states, in which the diagnosis and clinical decision-making are more difficult and challenging.**

Methods. **We analyzed 161 patients with aortic stenosis (96 males, 65 females, mean age 68 ± 9 years) and a low cardiac output (thermodilution cardiac index ≤ 2.5 l/min/m^2). All patients underwent both cardiac catheterization and echocardiography within 48 hours one of the other. The invasive Gorlin valve area was used as gold standard (severe aortic stenosis = Gorlin ≤ 0.8 cm^2). Echocardiographic indexes were assessed by an investigator who was unaware of the hemodynamic findings.**

Results. **The mean Gorlin aortic valve area was 0.7 ± 0.3 cm^2; cardiac catheterization allowed the identification of 129 patients with severe aortic stenosis and of 32 with mild-to-moderate aortic stenosis. The diagnostic accuracy of the Doppler gradient alone was low (sensitivity 55%). The best linear correlation with the Gorlin value was found using the "function-corrected" ejection fraction-velocity ratio (r = 0.85). Similarly, the best combination of sensitivity and specificity in identifying patients with severe aortic stenosis, as assessed by cardiac catheterization, was observed using the ejection fraction-velocity ratio (sensitivity 87%, specificity 88%).**

Conclusions. **In patients with aortic stenosis and a low cardiac output, the "function-corrected" ejection fraction-velocity ratio offers the better diagnostic accuracy, as compared with the cardiac catheterization valve area calculation.**

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Introduction

Which index of the severity of aortic stenosis could be considered best in clinical practice is a matter still under discussion[1]. In patients with a normal left ventricular function, very simple measures (i.e. a maximum Doppler velocity ≥ 4 m/s) are sufficient to indicate aortic valve replacement if symptoms should appear. The true problem, however, is the evaluation of the severity of aortic stenosis in patients with left ventricular dysfunction and a decreased cardiac output, in whom the jet Doppler velocity (or gradient) alone is inadequate[2,3]. Given the flow dependence of the transvalvular gradient itself, in the presence of a low cardiac output it is possible to observe a severe aortic valve stenosis also with a low pressure gradient. For this reason "flow-corrected" indexes have been developed in the cardiac catheterization laboratories since the 50's, when the Gorlin aortic valve area calculation and the aortic valve resistance (AVR) formula were validated to assess the severity of aortic stenosis[4,5]. Afterwards, another echocardiographic Doppler flow-corrected measure was introduced and widely used in clinical practice: the continuity equation (CE) valve area calculation[6-15]. In addition, in the last years it has been demonstrated that echocardiography allows a reliable noninvasive assessment of AVR[16-18].

Unfortunately, in several clinical conditions even the CE shows significant limitations. Measurements of the left ventricular outflow tract (LVOT) diameter and time-velocity flow integrals are time-consuming and may be technically difficult and inaccurate, especially in elderly patients with calcified aortic valve stenosis.

Other new interesting echocardiographic measures of the severity of aortic stenosis have been recently introduced. These indexes can be classified into two groups: 1) "function-corrected" indexes: the fractional shortening-velocity ratio (FSVR)[19-21] and the ejection fraction-velocity ratio (EFVR)[22]; 2) "pressure-corrected" indexes: the percent stroke work loss (PSWL)[23-26]. There is little information, however, about the true additional clinical relevance of these new severity indexes; in particular, it is unknown if these measures can be considered reliable in patients with aortic stenosis and a decreased cardiac output, in whom the diagnosis and clinical decision-making are more difficult.

Methods

Study population. From a series of 385 consecutive patients with aortic valve stenosis evaluated at cardiac catheterization, we analyzed the data of 161 patients with a thermodilution cardiac index $\leq$ 2.5 l/min/m^2. There were 96 men and 65 women with a mean age of 68 ± 9 years. All patients underwent two-dimensional and Doppler echocardiography within 48 hours of cardiac catheterization; all echo-Doppler examinations were performed by a sonographer who was unaware of the catheterization data. No patient had more than moderate aortic regurgitation as assessed at color Doppler imaging (aortic insufficiency was absent in 14 patients, mild in 107 patients, moderate in 40 patients). Mitral regurgitation was present in 156 patients (trivial-to-mild in 115, moderate-to-severe in 41 patients). Sinus rhythm and atrial fibrillation were present in 140 and 21 patients, respectively.

Echo-Doppler studies. Examinations were performed with the patient in the left lateral decubitus position using an Aloka 870 or 2200 ultrasound imaging unit (Aloka, Tokyo, Japan) or a Hewlett-Packard Sonos 2500 or Sonos 5500 equipped with 2.5-3.5 MHz phased array duplex transducers (Hewlett-Packard, Andover, MA, USA).

The CE valve area calculation was made, as previously described[6-8], as: aortic valve area = (area - LVOT) $\times$ (time-velocity integral - LVOT)/(time velocity integral - aortic jet). The area of the LVOT was calculated as [(diameter/2)^2 $\times$ π], assuming a circular shape; the inner LVOT diameter was measured, using digital calipers, from the trailing edge of the anterior echo to the leading edge of the posterior echo in the parasternal long-axis view just below the insertion of the anterior and posterior aortic valve leaflets during early systole. The LVOT velocities were measured at pulsed wave Doppler from an apical 4-chamber view angled anteriorly by positioning the sample volume 0.5 to 1.0 cm proximal to the aortic annulus. The sample volume was carefully moved up and down to obtain a stable audio and spectral signal thus avoiding the acceleration that occurs just proximal to the stenotic valve. The aortic jet was interrogated with continuous wave Doppler from multiple ultrasound views, in order to obtain the true maximal velocity. The maximal instantaneous gradient across the aortic valve and the mean gradient were derived from the aortic Doppler velocities by the modified Bernoulli's equation (pressure gradient = 4 $\times$ velocity^2). All velocities were averaged over 3 to 5 beats in sinus rhythm and over 8 to 10 beats in atrial fibrillation.

The AVR[21] was calculated as follows: AVR = [1.333 $\times$ (mean pressure gradient) $\times$ (systolic ejection period)/(area - LVOT) $\times$ (time-velocity integral - LVOT)].

As previously described[19], the FSVR was calculated as follows: FSVR = (percent left ventricular fractional shortening)/(peak Doppler-derived aortic gradient). The left ventricular fractional shortening was measured at M-mode echocardiography, using two-dimensional guidance, derived from the parasternal short-axis view at the mid-ventricular level just below the mitral leaflets from the end-diastolic and end-systolic diameters using the leading edge to leading edge convention.

Similarly, the EFVR[22] was calculated as follows: EFVR = (percent left ventricular ejection fraction)/(peak Doppler-derived aortic gradient). Two-dimensional ejection fraction was obtained from the apical 4-chamber view with aorta with a maximized left ventricular cavity by measuring the end-diastolic and end-systolic volumes using the area-length method or the modified Simpson's rule according to the recommendations of the American Society of Echocardiography[27].

The PSWL was calculated, as described by Tobin et al.[23], as follows: PSWL = (mean Doppler-derived aortic gradient)/(mean left ventricular systolic pressure). Mean left ventricular systolic pressure was approximated, as previously suggested, simply by adding the systolic arterial cuff pressure and the mean transvalvular gradient itself.

The degree of mitral and aortic regurgitation was evaluated by means of color Doppler flow mapping, as previously described[28,29].

Cardiac catheterization studies. All patients were submitted to mild sedation 1 hour before catheterization; otherwise there were no changes in medication between the noninvasive and invasive measurements. The left ventricular and ascending aortic pressures were recorded using fluid-filled catheters (7F or 6F) by the pullback technique from the left ventricle to the ascending aorta. The pressure gradient was assessed by superimposing the pressure recordings. Cardiac output was determined in all cases by the thermodilution technique; unless the first 3 measurements were very similar, values from 5 determinations were averaged. No patient had shunts or more than moderate tricuspid or pulmonary insufficiency. The aortic valve area was calculated using the Gorlin formula[4] as follows: [(cardiac output)/44.5 × (systolic ejection period) × (√mean systolic pressure gradient)].

Coronary arteriography was performed in all 161 patients. Significant stenosis (lumen narrowing ≥ 50% of the diameter) was found in 50 patients (31%).

Statistical analysis. Echo-Doppler and catheterization data were analyzed by independent observers. The results are expressed as means ± SD. The correlation between CE, AVR, FSVR, EFVR, PSWL and mean Doppler gradient and aortic valve area as determined at cardiac catheterization were respectively assessed using simple linear regression analysis. The gold standard Gorlin catheterization-derived aortic valve area was defined as follows: severe ≤ 0.80 cm^2, mild-to-moderate > 0.80 cm^2. As previously suggested[3], for the echocardiographic indexes the following were considered as cut-off values of severity: ≤ 0.80 for CE and EFVR, ≤ 0.50 for FSVR, ≥ 300 dynes × s × cm^{-5} for AVR, ≥ 23% for PSWL and ≥ 50 mmHg for the mean transvalvular Doppler gradient. On the basis of these definitions, the sensitivity, specificity and predictive value of the different indexes were calculated using standard formulas. Finally, a receiver operating characteristic (ROC) analysis was performed in order to better assess the performance of each index and the reliability of the conventional cut-off values of severity.

Results

The mean Gorlin aortic valve area was 0.7 ± 0.3 cm^2; at cardiac catheterization 129 patients with severe and 32 with mild-to-moderate aortic stenosis were identified. Table I shows the means ± SD and the range of Doppler echocardiographic and cardiac catheterization data. There were no statistically significant differences in heart rate and systolic and diastolic blood pressures when invasive and noninvasive examinations were compared.

The correlation analyses between the invasive Gorlin aortic valve area and the considered Doppler echocardiographic parameters are shown in figures 1 to 6. The less satisfactory correlation was found between the Gorlin valve area and the mean Doppler gradient (r = 0.74). Among corrected indexes, the best correlation with the invasive gold standard was observed using function-cor-

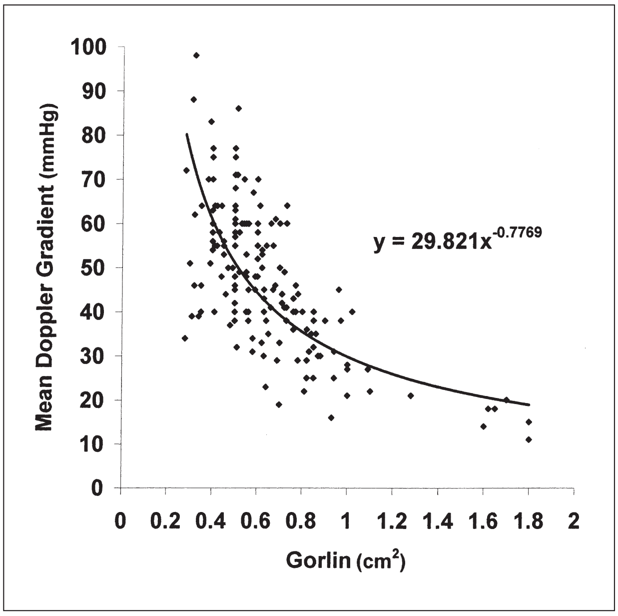

Figure 1. *Correlation between the mean aortic Doppler gradient and the catheterization-derived aortic valve area as measured using the Gorlin formula (r = 0.74).*

Table I. Doppler echocardiographic and cardiac catheterization data in the study population of 161 patients with aortic stenosis and a reduced cardiac output.

	Mean ± SD	Range
Doppler echocardiography		
Maximum aortic Doppler velocity (m/s)	4.4 ± 0.8	2.3-6.3
Maximum aortic gradient (mmHg)	81 ± 28	21-159
Mean aortic Doppler gradient (mmHg)	48 ± 16	11-98
Ejection fraction (%)	52 ± 12	14-74
Aortic valve area-continuity equation (cm^2)	0.76 ± 0.29	0.30-2.01
Ejection fraction-velocity ratio	0.73 ± 0.36	0.14-2.67
Fractional shortening-velocity ratio	0.42 ± 0.21	0.11-1.34
Aortic valve resistance (dynes × s × cm^{-5})	289 ± 129	56-764
Percent stroke work loss (%)	26 ± 8	7-49
Cardiac catheterization		
Peak-to-peak aortic gradient (mmHg)	64 ± 30	11-142
Ejection fraction (%)	56 ± 14	22-85
Cardiac output (l/min)	3.9 ± 0.6	2.1-5.6
Cardiac index (l/min/m^2)	2.1 ± 0.3	1.3-2.5
Aortic valve area-Gorlin (cm^2)	0.65 ± 0.28	0.28-1.80
Systolic blood pressure (mmHg)	132 ± 24	80-205
Diastolic blood pressure (mmHg)	66 ± 15	41-110

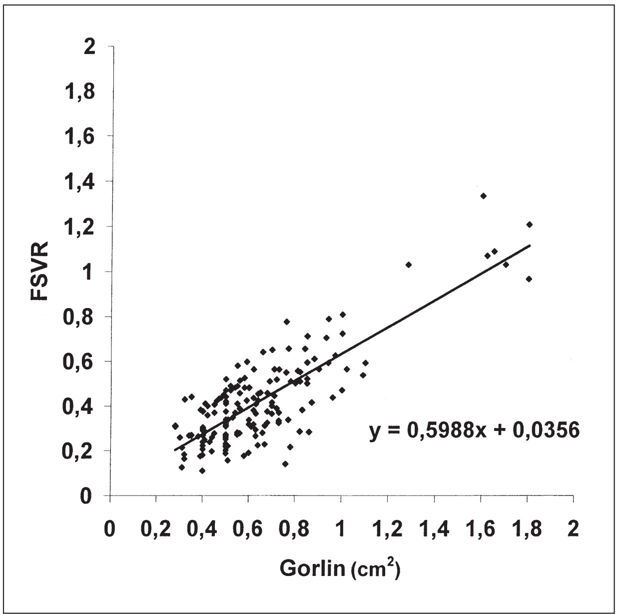

Figure 2. *Correlation between the fractional shortening-velocity ratio (FSVR) and the catheterization-derived aortic valve area as measured using Gorlin formula (r = 0.82).*

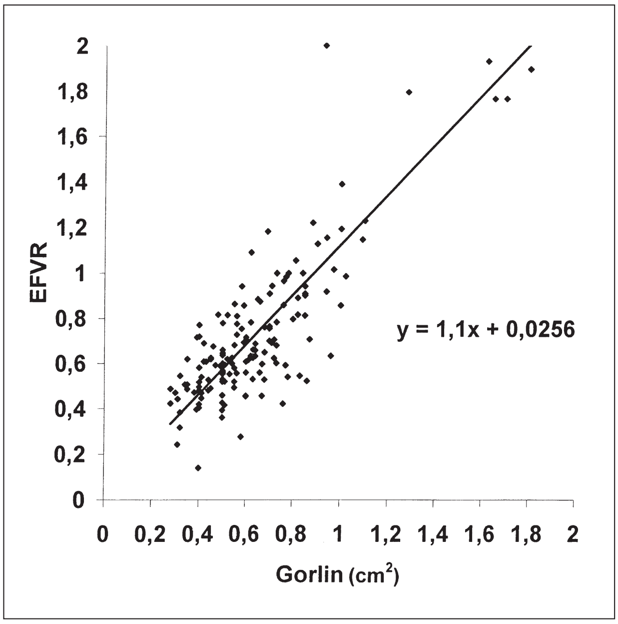

Figure 3. *Correlation between the ejection fraction-velocity ratio (EFVR) and the catheterization-derived aortic valve area as measured using the Gorlin formula (r = 0.85).*

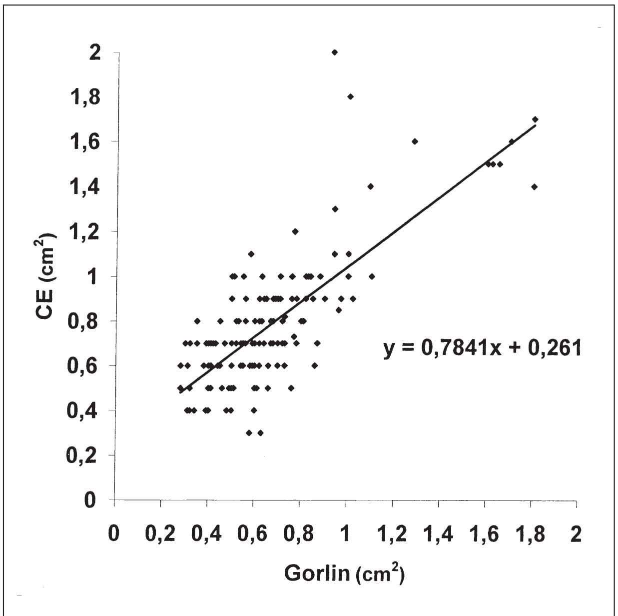

Figure 4. *Correlation between the noninvasive aortic valve area measured by the continuity equation (CE) and the catheterization-derived aortic valve area as measured using the Gorlin formula (r = 0.77).*

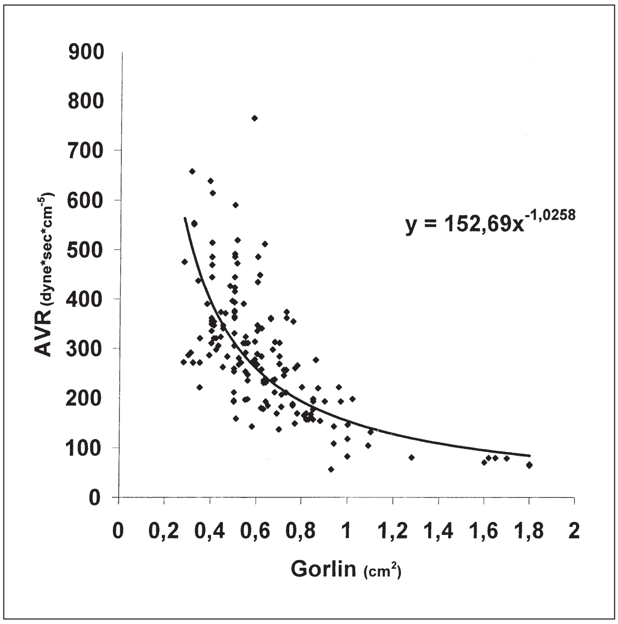

Figure 5. *Correlation between the aortic valve resistance (AVR) and the catheterization-derived aortic valve area as measured using the Gorlin formula (r = 0.77).*

rected indexes (linear correlation Gorlin-EFVR: r = 0.85; linear correlation Gorlin-FSVR: r = 0.82). Considering flow-corrected indexes, both the AVR and CE showed a correlation with the Gorlin formula (r = 0.77). Finally, when analyzing the pressure-corrected index, we found a nonlinear correlation Gorlin-PSWL (r = 0.74).

The diagnostic accuracy of all Doppler echocardiographic parameters is reported in table II: as expected, the sensitivity of a mean Doppler gradient ≥ 50 mmHg is inadequate (55%) in identifying patients with severe aortic stenosis. Among corrected indexes, the best combination of sensitivity and specificity was found using the function-corrected EFVR (sensitivity 87%, specificity 88%). To assess whether the presence of mitral regurgitation can significantly influence the reliability of new indexes, especially function-corrected ones, we separately analyzed the subgroup of 41 patients with moderate-to-severe mitral regurgitation. The diagnostic accuracy of all the Doppler-echocardiographic parameters in these patients is shown in table III.

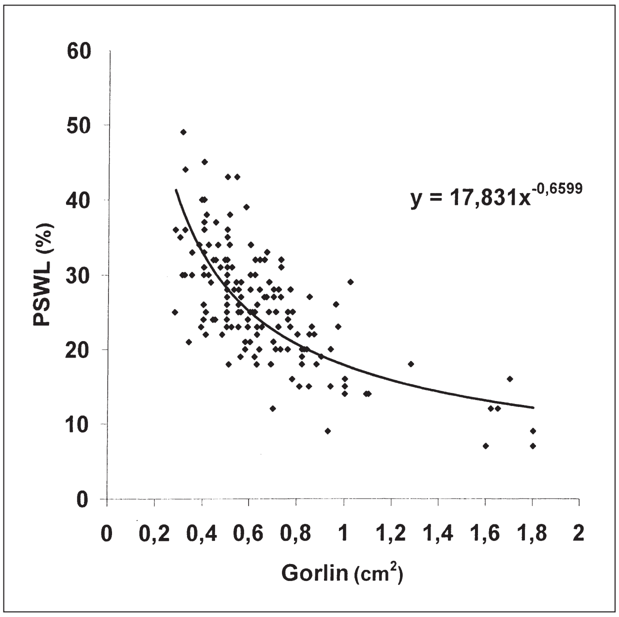

Figure 6. *Correlation between the percent stroke work loss (PSWL) and the catheterization-derived aortic valve area as measured using the Gorlin formula (r = 0.74).*

Table IV summarizes the results of the ROC analysis for each index, showing a generally good agreement between the invasive Gorlin measurements and the echocardiographic indexes (values of the area under the ROC curve ranging from 0.891 and 0.947). This analysis, however, confirms the unreliability of the cut-off point of 50 mmHg for the mean aortic gradient in this group of patients. Figure 7 shows the ROC comparison between EFVR and the Gorlin valve area.

Discussion

The accuracy of Doppler echocardiography in assessing the severity of aortic stenosis has been well established by several studies. Indeed, in clinical practice the CE method is now largely employed to calculate the effective aortic valve area and today in many institutions Doppler echocardiography is widely replacing cardiac catheterization for the assessment of the severity of aortic stenosis before aortic valve replacement[30-32]. The CE method, however, is time-consuming and sometimes inaccurate, requiring an exact measurement of both the diameter of the LVOT and of the subvalvular velocity at pulsed wave Doppler[21]. The reproducibility of the measurements of the subvalvular diameter is generally good in patients with a noncalcified aortic valve, but in patients with significant calcifications this measurement can be very difficult[33]. This fact is particularly important considering that today elderly persons with calcified aortic valve stenosis are by far the most commonly encountered subjects in clinical practice[34,35]. Furthermore, the errors in measuring the LVOT diameter are emphasized by the square elevation of the radius. Another limitation and source of variability is given by the recording of the velocity in the LVOT at pulsed wave Doppler; due to the axial movements of the aortic annulus during systole and to the skewness of the velocity distributions in the LVOT[36-39] it is very difficult to correctly localize the pulsed Doppler sample volume. Another point under discussion is the flow dependence of the CE that is intrinsic to the method, giving the flow correction contained in the formula itself[18].

Table II. Diagnostic accuracy of Doppler echocardiographic measures in identifying patients with severe aortic stenosis (invasive aortic valve area 0.8 cm^2) in 161 patients with a low cardiac output.

	Cut-off value	Sensitivity (%)	Specificity (%)
Mean aortic Doppler gradient	50 mmHg	55	100
Aortic valve area (continuity equation)	0.8 cm^2	83	90
Aortic valve resistance	300 dynes $\times$ s $\times$ cm^{-5}	81	89
Fractional shortening-velocity ratio	0.5	88	78
Ejection fraction-velocity ratio	0.8	87	88
Percent stroke work loss	23%	84	84

Table III. Diagnostic accuracy of Doppler echocardiographic measures in identifying patients with severe aortic stenosis (invasive aortic valve area 0.8 cm^2) in 41 patients with a low cardiac output and moderate-to-severe mitral regurgitation.

	Cut-off value	Sensitivity (%)	Specificity (%)
Mean aortic Doppler gradient	50 mmHg	45	100
Aortic valve area (continuity equation)	0.8 cm^2	73	75
Aortic valve resistance	300 dynes $\times$ s $\times$ cm^{-5}	76	75
Fractional shortening-velocity ratio	0.8	79	75
Ejection fraction-velocity ratio	0.5	79	87
Percent stroke work loss	23%	79	87

Table IV. Receiver operating characteristic (ROC) analysis. Comparison between the Gorlin valve area (cut-off point of severity ≤ 0.8 cm^2) and Doppler echocardiographic measures in 161 patients with aortic stenosis and a low cardiac output.

	Best cut-off value	Area under the ROC	Sensitivity (%)	Specificity (%)
Mean gradient	38 mmHg	0.947	86	90
Continuity equation	0.82 cm^2	0.915	84	90
Aortic valve resistance	276 dynes $\times$ s $\times$ cm^{-5}	0.891	87	81
Fractional shortening-velocity ratio	0.4891	0.894	81	82
Ejection fraction-velocity ratio	0.8108	0.911	88	87
Percent stroke work loss	22%	0.915	84	84

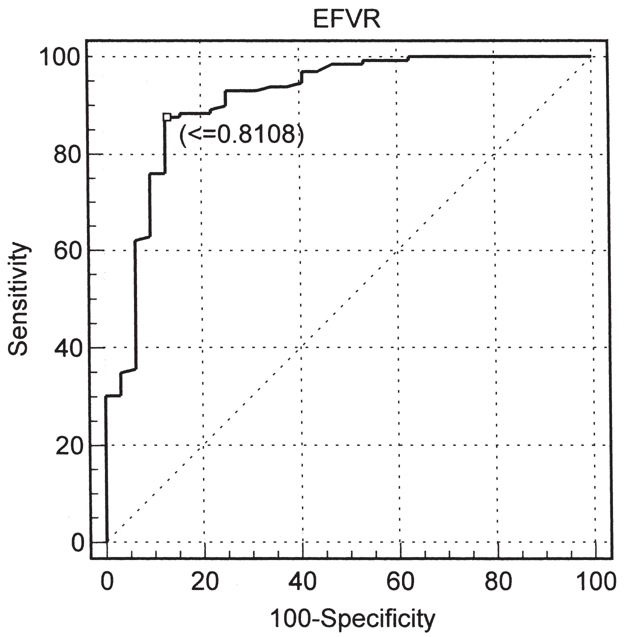

Figure 7. *Receiver operating characteristic curve comparison between the Gorlin valve area and the ejection fraction-velocity ratio (EFVR). The area under the receiving operator curve is 0.911. The best cut-off point to identify Gorlin valve area values < 0.80 cm^2 is 0.82 (sensitivity 88%, specificity 87%).*

In order to overcome the limitations of the CE, other indexes for the assessment of the severity of aortic stenosis have recently been introduced. A classification of old and new measures into three groups on the basis of the "corrections" respectively used has recently been proposed[3]: flow-correction: CE and AVR; pressure-correction: PSWL; function-correction: FSVR and EFVR. To date, however, little was known about the reliability of each of these measures in patients with aortic stenosis and a decreased cardiac output, in whom both the diagnosis and clinical decision-making are more difficult.

The present study, including patients with aortic stenosis and a significantly reduced cardiac output, confirms the poor sensitivity of Doppler velocity alone in identifying patients with severe aortic stenosis[40]. In this situation, indeed, the presence of a severe aortic stenosis does not always imply a high transvalvular gradient, because the gradient itself is strictly flow-dependent. In terms of the correlation with the catheterization-derived aortic valve area and of diagnostic accuracy, the function-corrected indexes, particularly EFVR, were superior in identifying severe aortic stenosis to flow-dependent and pressure-dependent ones.

Furthermore, the EFVR method, recently validated in a large population of unselected patients with aortic stenosis[22], offers the advantage of simplicity since it does not necessitate all the difficult and sometimes boring LVOT measurements. The EFVR is the simple ratio of two-dimensional ejection fraction and maximum aortic Doppler gradient. It is noteworthy that both ejection fraction and maximum gradient are routinely measured in every standard echocardiographic study; so the method is virtually nontime-consuming. With regard to this, we preferred a monoplane method to calculate the ejection fraction; however, it should be borne in mind that monoplane measurements may be inaccurate in some patients, especially those with regional wall motion abnormalities. Another practical advantage of EFVR is the similarity of the results with the effective valve area for values < 1.5 cm^2 (it must be recognized that for larger orifice areas the relationship between EFVR and the area tends to become nonlinear, but this discrepancy is not clinically relevant in routine practice because these cases are easily identified as mild ones). On the other hand, a theoretical limitation of the function-corrected EFVR could be related to the use of ejection fraction as an indirect index of transaortic valve flow in patients with aortic stenosis and associated significant mitral regurgitation. In this subgroup of patients the EFVR might be expected to yield an increase in false negative cases because the values for this ratio would be erroneously high due to the increased ejection fraction observed in significant mitral regurgitation. In the subgroup of 41 patients with coexisting moderate or severe mitral regurgitation, however, both the sensitivity and specificity were still acceptable (79 and 87% respectively).

It is noteworthy that some patients had a normal ejection fraction despite a reduced cardiac index (40 patients showed an ejection fraction > 60% in our series). This apparent discrepancy can be explained if one considers that 6 of these patients had moderate mitral regurgitation; other patients had concentric hypertrophy with "small" left ventricles and relative sinus bradycardia, resulting in a low cardiac output. Even in these patients, however, the function-corrected indexes were found to have a good diagnostic accuracy.

Among function-corrected indexes, the EFVR, despite the monoplane measurement, showed a higher diagnostic accuracy for the assessment of the severity of aortic stenosis, as compared with the FSVR, probably due to the unreliability of fractional shortening in patients with regional wall motion abnormalities, conduction defects or pacemakers, common conditions in our population of elderly patients with a reduced cardiac output.

Conventional flow-corrected indexes (CE, AVR) were found to be well correlated with invasive valve area measurements (but slightly inferior to the EFVR, despite the fact that they are theoretically more similar to the Gorlin formula). Probably, the lower diagnostic accuracy is secondary to technical reasons, in particular to the measurement of LVOT diameter in patients with heavy calcifications of the aortic cusps.

It must be recognized that even the pressure-corrected PSWL offered a good diagnostic accuracy in identifying patients with severe aortic stenosis, as assessed by cardiac catheterization (sensitivity 84% and specificity 84%). The advantage of the PSWL, similarly to the EFVR, is the absolute simplicity of the method, requiring just the measurement of the Doppler gradient and of the cuff systolic blood pressure.

ROC analysis showed a good agreement between the invasive aortic valve area measurements and all the echocardiographic indexes (values of the area under the ROC curve ranging from 0.895 to 0.947). This analysis, however, confirms the absolute unreliability of the cut-off point of 50 mmHg for the mean aortic gradient in this group of patients, while for the other indexes the conventional cut-off points of severity and the ROC-suggested cut-off points are very similar.

Clinical implications. The present study confirms the unreliability of Doppler velocity alone in predicting the hemodynamic severity of aortic stenosis in low-flow states; therefore, it is absolutely necessary that "corrected" indexes must be used for clinical decision-making in this particular situation.

In patients with a reduced cardiac output, the function-corrected EFVR seems to be the best index for identifying patients with severe aortic valve stenosis, as compared with cardiac catheterization measurements. The EFVR is a nondimensional index of the severity of aortic stenosis that correlates very well with the aortic valve area, but it may be considered as a functional parameter of hemodynamic impairment which takes into account the ejection fraction and maximum Doppler-derived gradient. It is interesting that in the study of Pellikka et al.[41] on the natural history of patients with asymptomatic aortic stenosis, the authors observed that the peak Doppler velocity and ejection fraction were the factors which most accurately predicted the risk of developing symptoms and experiencing cardiac events. It is reasonable to presume that the EFVR, incorporating both the ejection fraction and the Doppler velocity into a single formula, can provide further important clinical information in the echocardiographic follow-up of these patients. Even the PSWL shows a good diagnostic accuracy, comparable to that of conventional flow-corrected measures.

Given the high diagnostic accuracy and the easiness to measure, the EFVR and PSWL may be used as independent methods for the assessment of the severity of aortic stenosis even in patients with a low cardiac output, at least in those cases in which the CE valve area calculations are technically difficult to obtain. The EFVR and the PSWL methods may also be used as adjunctive, nontime-consuming and reliable methods in all controversial and equivocal cases.

Finally, it is unclear whether the EFVR could be less flow-dependent than other indexes such as CE, AVR or PSWL. Further stress echocardiographic studies are probably needed to understand whether the EFVR can offer adjunctive useful prognostic information in patients with aortic stenosis, a depressed left ventricular function and low transvalvular gradients.

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