

Comparison of Valve Resistance With Effective Orifice Area Regarding Flow Dependence

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Aortic valve resistance has been proposed to represent the severity of aortic stenosis because some studies observed that it was less affected by change in flow than the valve-effective orifice area, but this issue remains controversial. The objective of this study was to systematically analyze the theoretical and practical determinants of these parameters in relation to changes in flow. Valve area and resistance in different valves were studied in vitro in a pulse duplicator system at different flow rates and in vivo in 90 subjects referred to either exercise or dobutamine infusion. Theoretical analysis and experimental results both demonstrated a unique relation between resistance (RES), valve-effective orifice area (EOA), and flow rate (Q): $RES = K \times (Q/EOA^2)$. Accordingly, in fixed stenoses or in mechanical valves,

resistance increased markedly with flow rate both in vitro ($+0.88 \pm 0.26\%/%$ of flow increase) and in vivo (mechanical valves: $+2.09 \pm 4.61$, fixed stenotic valves: $+0.59 \pm 0.32\%/%$), whereas valve area did not change significantly ($<0.2\%/%$). In contrast, in valves with a flexible orifice (bioprostheses and some patients with aortic stenosis), resistance was less increased due to the increase in valve area. Thus, both from a theoretical and a practical standpoint, valve resistance is much more flow dependent than valve area, particularly in fixed stenoses. Situations in which resistance does not increase with flow rate are unpredictable and are found in flexible valves when there is a concomitant increase in valve area. ©2001 by Excerpta Medica, Inc.

(Am J Cardiol 2001;88:45–52)

Transvalvular pressure gradient (TPG) and valve-effective orifice area (EOA) are the parameters most often used to assess aortic valves. However, EOA calculated by hydraulic formulas is not necessarily a fixed variable but often increases with an increase in transvalvular flow,^{1–9} and it has been suggested that this may be due to an error in the formula used to calculate the EOA rather than to an actual increase in area.¹ In this context, valve resistance (RES) has been proposed as an alternate mean of characterizing aortic stenosis because it may be less flow dependent^{1,7,8,10–13}; however, other studies in mechanical valves and fixed stenoses have suggested the contrary.^{14,15} We therefore elected to systematically analyze the variations in resistance and EOA occurring during changes in flow using both in vitro and in vivo protocols to better understand the pathophysiology underlying these parameters.

METHODS

In vitro study: A mock flow circulation model previously described in detail^{16,17} was used and studies

were performed in 2 bioprosthetic valves (Medtronic Mosaic 21 and 25 mm, Medtronic, Inc., Minneapolis, Minnesota), 2 mechanical bileaflet valves (St. Jude HP 21 and 25 mm, St. Jude Medical, Inc., St. Paul, Minnesota), and 2 fixed stenoses (2 plates with circular orifices of 1.0 and 1.5 cm²). These valves were tested under 5 stroke volumes: 32 ± 2 , 58 ± 3 , 74 ± 5 , 91 ± 8 , and 115 ± 13 ml, with an ejection time of 400 ± 25 ms. Catheter measurements of left ventricular (LV) and aortic pressures were performed 20 mm upstream and 60 mm downstream to the valve, respectively. The Doppler-derived mean gradient was calculated using the modified Bernoulli equation. Valve EOA was determined by the standard continuity equation using the stroke volume measured by electromagnetic flowmeter. Valve RES was calculated using the formula¹¹:

$$RES = \frac{1333 \times TPG_{mean}}{Q} \quad (1)$$

where TPG_{mean} is the mean TPG in mm Hg, and Q the mean transvalvular flow rate in ml/s. Resistance was calculated by both catheter and Doppler.

In vivo study: Ninety patients (78 men and 12 women, aged 22 to 81 years) were studied. In 63 patients with different types of valve replacement (13 stented bioprostheses, 16 stentless bioprostheses, 14 bileaflet mechanical valves, 20 pulmonary autografts) and in 10 normal control subjects, a graded exercise protocol was used, whereas a dobutamine infusion protocol was performed in 17 patients with aortic stenosis. Twelve patients had moderate stenosis (EOA range 1.05 to 1.42 cm²) and 5 patients had severe stenosis (0.68 to 0.99 cm²). Of the 17 patients, 5 had

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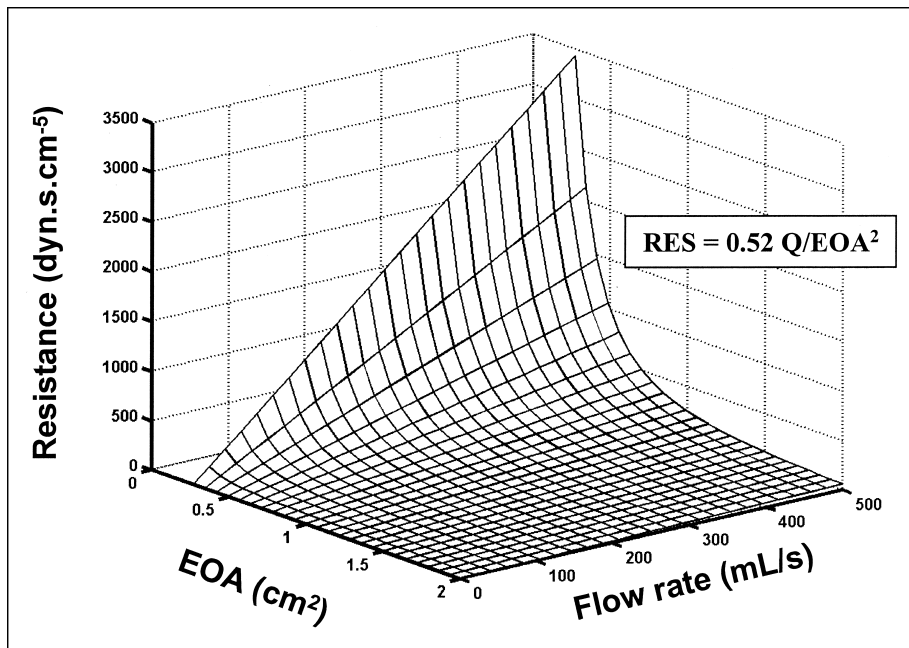


FIGURE 1. Theoretical relation between RES, valve EOA, and transvalvular flow rate.

a low LV ejection fraction (<40%). Control subjects were healthy volunteers with no evidence of heart disease.

Exercise protocol consisted of a maximal ramp upright bicycle exercise test with workload increments between 15 and 35 W/min depending on subject's physical condition. Patients were encouraged to exercise until exhaustion or appearance of symptoms. Test was also stopped if there was an abnormal increase or decrease in blood pressure, electrocardiographic evidence of ischemia, or significant arrhythmia. Doppler echocardiographic measurements were obtained with the patient sitting on the bicycle, and were done at rest and within 2 minutes after the cessation of exercise.¹⁸

The dobutamine infusion protocol was designed to obtain incremental increases in flow and a steady state at each level. It consisted of 15-minute increments of 2.5 $\mu\text{g}/\text{kg}/\text{min}$ up to a maximum dosage of 10 $\mu\text{g}/\text{kg}/\text{min}$; reported values for the Doppler echocardiographic measurements are those recorded before the infusion and at maximal dosage.

Baseline Doppler echocardiographic measurements included transvalvular flow velocity using continuous-wave Doppler, LV outflow tract flow velocity using pulsed-wave Doppler, and LV outflow tract diameter as previously described.^{18,19} The same measurements were obtained at the end of protocol except for LV outflow tract diameter, which was assumed to have remained constant.^{18,20} LV stroke volume was calculated from the product of the LV outflow tract velocity-time integral and cross-sectional area, mean transvalvular flow rate from the quotient of stroke volume and systolic ejection time, mean TPG using the modified Bernoulli equation with inclusion of pre-valvular velocities, EOA using the standard continuity equation, and valve RES using equation (1). The Doppler echocardiographic measurement of EOA during exercise has been previously validated.^{18,21} Al-

though the validity and reproducibility of the Doppler echocardiographic measurement of resistance during dobutamine or exercise were not confirmed, resistance was calculated using the same raw data as for EOA calculation.

Theoretical considerations: The following equations give the theoretical relations between EOA, flow, and resistance. Equation (2) is a variant of the Gorlin equation²²:

$$\text{EOA} = \frac{Q}{50 \times \sqrt{\text{TPG}_{\text{mean}}}} \quad (2)$$

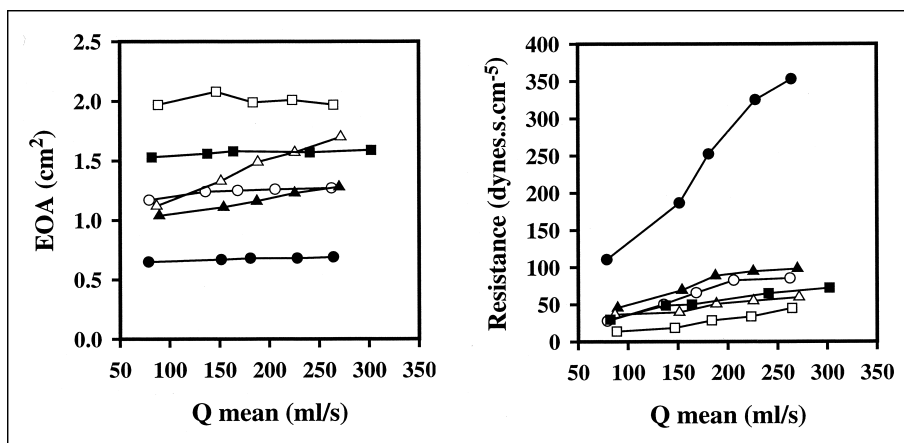
Equation (3) is another expression of resistance that is obtained by combining the equations 1 and 2:

$$\text{RES} = \frac{0.52 \times Q}{\text{EOA}^2} \quad (3)$$

The unique relation between resistance, flow, and EOA given by equation (3) is represented by the 3-dimensional graphic illustrated in Figure 1, from which it becomes obvious that resistance, as it is calculated, necessarily increases linearly with flow. Moreover, this flow dependence of resistance increases exponentially as EOA gets smaller, given that the denominator of the equation is the square of EOA. The graphic also shows that the relation between flow and EOA is horizontal and that unless there is an actual change in EOA, there is no mathematic reason for EOA to vary in response to a change in flow.

Statistical analysis: Changes in valve EOA and resistance with flow rate are expressed as relative percent change per percent change in flow rate. Data are expressed as mean \pm SD and compared using an analysis of variance for repeated measures to evaluate the effect of exercise/dobutamine and the effect of valve/stenosis group. Statistical analysis of the asso-

FIGURE 2. Changes in EOA (left panel) and valve RES (right panel) as a function of transvalvular flow rate in 2 fixed stenoses (1.00 cm², closed circles; 1.50 cm², open circles), 2 stented bioprostheses (Mosaic 21, closed triangles; Mosaic 25, open triangles), and 2 mechanical prostheses (St Jude 21, closed squares; St Jude 25, open squares) tested in an in vitro model.



ciation of variables was performed with the Pearson correlation coefficient or the determination coefficient when the relation was linear or nonlinear, respectively. Graphs were constructed with the corresponding regression equation using the Matlab software (version 5.3, The Mathworks Inc., Natick, Massachusetts). A p value <0.05 was considered significant.

RESULTS

In vitro study: In all valves and stenoses, an excellent correlation between Doppler and catheter measurements of TPG ($r = 0.99$, $SEE = \pm 1.59$ mm Hg) and valve RES ($r = 0.98$, $SEE = \pm 10$ dynes \cdot s \cdot cm⁻⁵) was found. However, the Doppler TPG (Doppler TPG = $1.50 + 1.28 \times$ catheter TPG) and thus the Doppler resistance (Doppler resistance = $11 + 1.24 \times$ catheter resistance) were consistently higher than those measured by catheter likely due to the relatively small aortic root (30 mm) of our model and the pressure recovery occurring downstream to the valve.^{17,23,24} The discrepancy between Doppler and catheter TPGs (and thus between Doppler and catheter resistances) was more important in mechanical valves (Doppler TPG = $-0.21 + 1.80 \times$ catheter TPG; $r = 0.99$, $SEE = \pm 0.71$ mm Hg) likely due to the presence of localized high TPG within the central valvular orifice. Given the high correlation between catheter- and Doppler-derived resistances and the fact that resistance was only measured by Doppler in patients, data reported hereafter are those obtained by Doppler.

Figure 2 illustrates the changes in valve EOA and resistance during the graded increases in mean flow rate. As is observed, EOA did not increase much with flow with regard to fixed stenoses ($+0.03 \pm 0.01\%/%$ increase in flow) and mechanical prostheses ($+0.01 \pm 0.01\%/%$), whereas it increased only moderately in the case of bioprostheses ($+0.18 \pm 0.09\%/%$). These results are expected because bioprostheses are semi-rigid and probably open more gradually in response to an increase in flow than fixed stenoses or mechanical prostheses. In contrast, resistance increased markedly with flow in all cases: fixed stenoses, $+0.91 \pm 0.02\%/%$; mechanical prostheses, $+0.85 \pm 0.45\%/%$; and bioprostheses, $+0.44 \pm 0.19\%/%$. In mechanical prostheses, the resistance measured by the catheter

also increased markedly with flow: $+1.2 \pm 0.9\%/%$. The most striking difference between EOA and resistance was observed in the 1.0 cm² fixed stenosis in which EOA increased only by $+0.03\%/%$ and resistance increased by $+0.93\%/%$. The flow-related increase in resistance was similar when the stroke volume increased from 32 to 74 ml (from low to normal flow, $+0.99\%/%$) than when it increased from 74 to 115 ml (from normal to high flow, $+0.87\%/%$).

In vivo study: Table 1 lists the demographic, resting and exercise, or dobutamine Doppler echocardiographic data for the various groups included in the in vivo study. As in the in vitro study, EOA did not increase in mechanical prostheses ($-0.09 \pm 0.57\%/%$ increase in flow; $p = 0.22$) and only slightly in stented ($+0.15 \pm 0.32\%/%$; $p = 0.038$) and stentless ($+0.15 \pm 0.17\%/%$; $p = 0.004$) bioprostheses (Figure 3). Also, EOA did not change in autografts ($-0.01 \pm 0.18\%/%$; $p = 0.73$) and normal controls ($+0.02 \pm 0.26\%/%$; $p = 0.62$), probably because these valves are much more compliant than bioprostheses and their opening is already maximal at the lower flow rate. On average, resistance increased with flow in all groups except in the group of patients with aortic stenosis (Figure 3). As observed in vitro, this increase varied depending on the type of valve: mechanical prostheses, $+2.09 \pm 4.61\%/%$ ($p = 0.002$); stented bioprostheses, $+0.95 \pm 1.31\%/%$ ($p = 0.006$); stentless bioprostheses, $+0.56 \pm 0.46\%/%$ ($p = 0.003$); autografts, $+1.30 \pm 0.63\%/%$ ($p < 0.001$); and normal controls $+1.50 \pm 1.46\%/%$ ($p < 0.001$). An example of the complete dissociation we observed between the changes in EOA and the changes in resistance is found in the mechanical prostheses where the EOA did not change significantly but the resistance increased by 2% of flow increase.

On average, the valve EOA in patients with aortic stenosis increased by $+0.53 \pm 0.74\%/%$ ($p < 0.001$), whereas resistance did not change significantly ($+0.04 \pm 0.98\%/%$; $p = 0.09$). However, we observed 2 different patterns of changes in EOA and resistance among these patients. Hence in Figure 4, we divided the patients according to whether their EOA increased by $\geq 10\%$ ("flexible stenosis") or $< 10\%$ ("fixed stenosis") during the increase in flow. In ex-

TABLE 1 Demographic, Resting, and Exercise or Dobutamine Doppler Echocardiographic Data in Normal Controls, Patients With Aortic Stenosis, and Patients With Different Types of Aortic Valve Substitutes: Pulmonary Autograft, Stented Bioprosthesis, Stentless Bioprosthesis, or Mechanical Prosthesis

	Normal Controls (n = 10)	Pulmonary Autograft (n = 20)	Stentless Bioprosthesis (n = 16)	Stented Bioprosthesis (n = 13)	Mechanical Prosthesis (n = 14)	Aortic Stenosis (n = 17)	p Value Effect of Exercise/Dobut.	p Value Effect of Valve Group
Age (yrs)	46 ± 10 ^{§ ¶**}	46 ± 10 ^{§ ¶**}	64 ± 7 ^{††}	64 ± 11 ^{††}	66 ± 11 ^{††}	62 ± 15 ^{††}	—	<0.001
Gender								NS
Women	2 (20%)	2 (10%)	1 (6.3%)	4 (30.8%)	2 (14.3%)	1 (5.9%)	—	NS
Men	8 (80%)	18 (90%)	15 (93.8%)	9 (69.2%)	12 (85.7%)	16 (94.1%)	—	NS
BSA (m ²)	1.87 ± 0.14	1.86 ± 0.20	1.84 ± 0.15	1.70 ± 0.28	1.92 ± 0.16	1.86 ± 0.12	—	NS
Mean flow rate (ml/s)							<0.001	NS
Rest	269 ± 53	270 ± 61	240 ± 38	256 ± 52	275 ± 66	254 ± 72		
Exercise/dobutamine	477 ± 136 ^{*¶}	449 ± 136 ^{*¶}	377 ± 69 [*]	376 ± 110 [*]	317 ± 82 ^{*††}	389 ± 137 [*]		<0.001
Mean gradient (mm Hg)							<0.001	<0.001
Rest	3 ± 1 ^{**}	3 ± 1 ^{**}	7 ± 4 ^{**}	15 ± 6 ^{††§ ¶}	9 ± 3 ^{**}	25 ± 7 ^{††§ ¶}		<0.001
Exercise/dobutamine	10 ± 5 ^{* **}	9 ± 4 ^{* **}	14 ± 8 ^{* **}	28 ± 12 ^{*††§ ¶**}	15 ± 6 ^{* **}	42 ± 18 ^{*††§ ¶}		<0.001
Effective orifice area (cm ²)							<0.001	<0.001
Rest	3.37 ± 0.74 ^{§ ¶**}	3.43 ± 0.92 ^{§ ¶**}	2.15 ± 0.45 ^{†† **}	1.44 ± 0.32 ^{††§}	2.09 ± 0.39 ^{††**}	1.06 ± 0.21 ^{††§¶}		<0.001
Exercise/dobutamine	3.43 ± 0.79 ^{§ ¶**}	3.46 ± 1.02 ^{§ ¶**}	2.40 ± 0.61 ^{†† **}	1.59 ± 0.52 ^{††§}	2.03 ± 0.41 ^{††**}	1.30 ± 0.33 ^{*††§¶}		<0.001
Resistance (dynes · s · cm ⁻⁵)							<0.001	<0.001
Rest	15 ± 6 ^{**}	16 ± 10 ^{**}	39 ± 19 ^{**}	81 ± 37 ^{††§ ¶**}	44 ± 14 ^{**}	134 ± 32 ^{††§ ¶}		<0.001
Exercise/dobutamine	29 ± 9 ^{* **}	28 ± 17 ^{* ¶**}	50 ± 28 ^{* **}	109 ± 59 ^{*††§ ¶**}	64 ± 22 ^{* ¶**}	147 ± 49 ^{*†† ¶}		<0.001

*p < 0.05, rest versus exercise/dobutamine; significant difference between valve groups (p < 0.05); †significant difference versus controls; ‡versus autografts; §versus stentless; ||versus stented; ¶versus mechanical prostheses; **versus aortic stenosis. Values are expressed as mean ± SD. Dobut. = dobutamine.

FIGURE 3. Changes in EOA (left panel) and valve RES (right panel) as a function of transvalvular flow rate in normal control subjects (open circles) and in patients with a native aortic stenosis (filled octagons), a stented bioprosthesis (closed inverted triangles), a stentless bioprosthesis (open triangles), a mechanical prosthesis (closed squares), or a pulmonary autograft (open diamond).

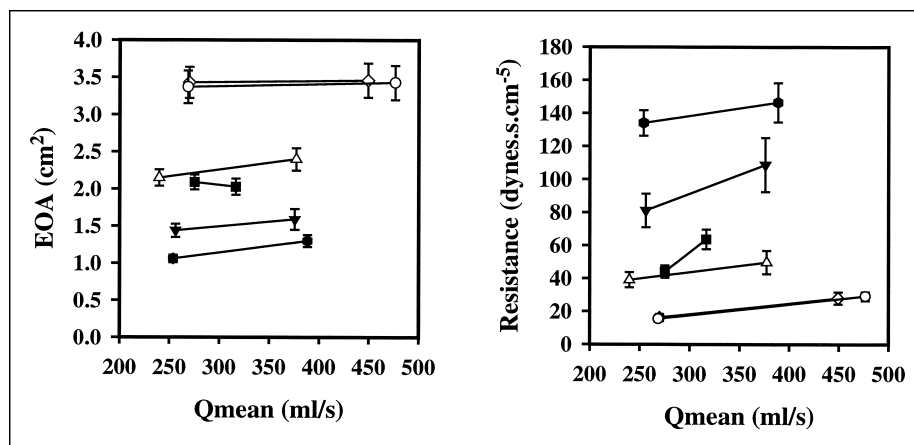
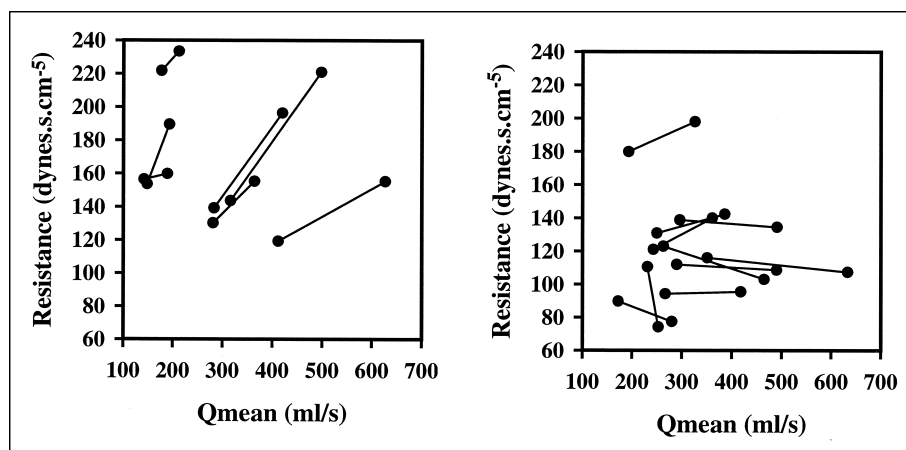


FIGURE 4. Individual changes in valve RES as a function of the flow rate increases in patients with a fixed aortic valve stenosis as defined by a percent increase in EOA <10% (left panel) versus in patients with a flexible stenosis (defined as a change in EOA ≥10%) (right panel).



performed in clinical laboratories, the reproducibility of a continuity equation valve EOA measurement is 5% to 8%, so that a relative change of >10% during exercise or dobutamine infusion can therefore be considered as clinically significant.²⁵ There was no significant difference between patients with flexible stenoses and those with fixed stenoses with regard to flow (256 ± 51 vs 251 ± 100 ml/s⁻¹), valve EOA (1.11 ± 0.16 vs 1.00 ± 0.27 cm²), or valve RES (122 ± 25 vs 152 ± 33 dynes · s · cm⁻⁵) at baseline, as well as with regard to flow (410 ± 114 vs 358 ± 170 ml/s⁻¹) during dobutamine. As expected, the valve EOA during dobutamine was significantly larger (1.47 ± 0.24 vs 1.06 ± 0.30 cm²; $p = 0.004$) and resistance smaller (118 ± 37 vs 187 ± 32 dynes · s · cm⁻⁵, $p = 0.001$) in flexible stenoses. Although percent change in flow during dobutamine was lower in the fixed stenoses ($+39 \pm 14\%$ vs $+59 \pm 20\%$, $p = 0.032$), resistance increased much more in fixed stenoses ($+25 \pm 19\%$ in absolute terms or $+0.59 \pm 0.32\%/%$ increase in flow; $p = 0.01$) compared with flexible stenosis ($-4 \pm 14\%$ in absolute terms or $-0.34 \pm 1.11\%/%$; $p = 0.53$).

Relation to theoretical background: In Figure 5, the experimental results for resistance are plotted against EOA and flow rate. The graphs and the regression equations that are obtained with these in vitro (panel A) and in vivo (panel B) experimental data are very similar to the theoretical graph (Figure 1) and Equa-

tion 3. Moreover, the regression equations based on EOA and flow rate were able to explain >95% of the variation of the valve RES both in vitro ($r^2 = 0.99$) and in vivo ($r^2 = 0.95$). Also, Figure 1 illustrates the following basic observations: (1) resistance is intrinsically flow dependent in the presence of a fixed stenosis, (2) the flow dependence of resistance increases exponentially as the EOA gets smaller, (3) the only instances in which resistance increases less than expected with flow are those when there is also a concomitant increase in EOA.

DISCUSSION

The results of this study are best understood by reexamining the mathematic formulas used to calculate EOA and resistance. Hence, equation (2) shows that there is no intrinsic reason for EOA to change with flow because both the numerator and denominator vary in the same proportion with a change in flow. In contrast, equation (3) shows that, per se, an increase in flow (Q) will necessarily result in an increase in resistance, unless it is compensated by a concomitant increase in EOA. Moreover, because the denominator is EOA squared, the flow dependence of resistance increases exponentially as the EOA gets smaller. This finding is in agreement with the study by Takeda et al²⁶ showing that the TPG/flow slope varies markedly

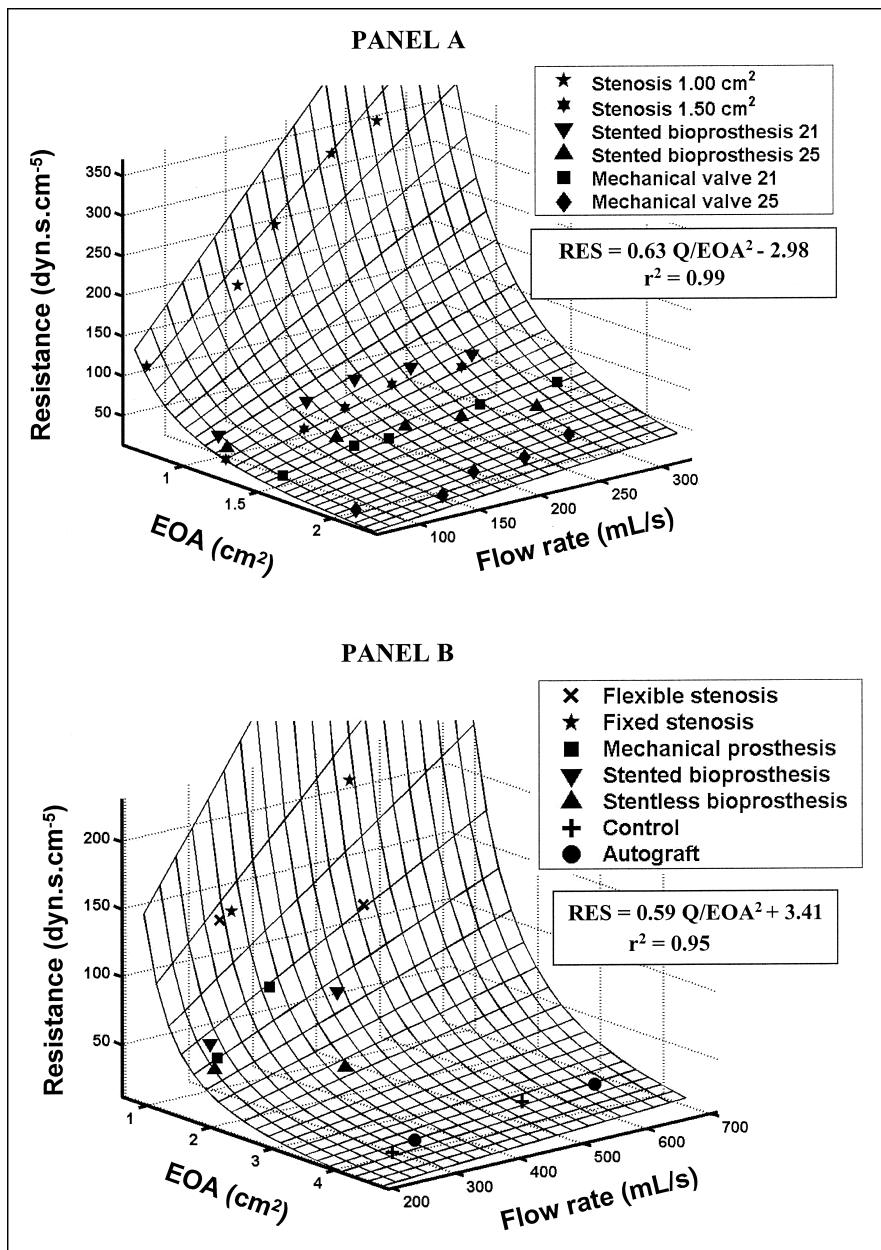


FIGURE 5. Correlation between valve RES, EOA, and transvalvular flow rate. Panels A and B show this relation for the experimental results obtained in vitro and in vivo, respectively. For more clarity, panel B shows the curve fitting obtained in all patients as well as 1 representative patient for each category of valve.

in individual patients with native aortic stenosis and that it is steeper in patients with small EOAs.

In this context, the curvilinear relation between EOA and resistance shown in Figures 1 and 5 has previously been observed in many studies.^{3,6,8,10,11} All these results are therefore evidence that the relation between EOA and resistance given by equation (3) is indeed a valid one. A major contribution of this study, however, is to provide a systematic analysis of how this relation is affected by changes in flow. In contrast, previous studies reporting that EOA is more flow dependent than resistance were mostly based on empirical observations in patients with native aortic stenosis.^{1,7,8,11} Considering the results of the present study, it would appear plausible that many of these patients could have had a flexible stenosis. Accordingly, the increase in EOA noted with the increase in

flow was probably a true reflection of reality, and the observation that resistance increased less with flow was likely due to this concomitant increase in EOA. Moreover, when individual data are made available in these studies, it is obvious that the response of EOA and resistance to flow is variable, and likely depends on the degree of flexibility of the stenosis. In contrast, studies in mechanical prostheses^{14,15} or in fixed stenosis²⁷ all conclude to the opposite, i.e., that resistance is more flow dependent than EOA. However, these apparent discrepancies are easily reconciled if one considers the 3 variable relations given by equation (3). Thus, it becomes obvious that the relations between flow and EOA or between flow and resistance cannot be considered separately and that resistance increases less with flow only if there is a concomitant increase in EOA.

TABLE 2 Theoretical Comparison of Valve Resistance in Six Hypothetical Patients Having the Same Valve Area But Different Body Surface Areas

	Patient Number					
	1	2	3	4	5	6
Body surface area (m ²)	1.50	1.75	2.0	1.50	1.75	2.0
Cardiac index (L/min/m ²)	3.00	3.00	3.00	1.50	1.50	1.50
Effective orifice area (cm ²)	0.65	0.65	0.65	0.65	0.65	0.65
Indexed effective orifice area (cm ² /m ²)	0.43	0.37	0.33	0.43	0.37	0.33
Mean transvalvular gradient (mm Hg)	43	59	77	11	15	19
Resistance (dynes · s · cm ⁻⁵)	270	316	361	135	158	180

The resistance can be calculated by either equation 1 or 3. For the purpose of this simulation, mean transvalvular flow rate was calculated assuming a heart rate of 60 beats/min and a systolic ejection time of 350 ms in the 6 patients. Patients 1, 2, and 3 have normal cardiac output, whereas patients 4, 5, and 6 have low output.

Finally, this study also underlines the difficulty of using valve RES as a stand-alone parameter for evaluating aortic valve stenosis severity. In Table 2, we hypothesized results in 6 patients with the same EOA and different body surface areas. If cardiac index is normal (patients 1, 2, and 3), the values for resistance and pressure gradients increase in relation to body surface area, consistent with a higher cardiac output and more severe hemodynamic consequences in the larger patients. In this context, valve RES, pressure gradient, and the indexed valve EOA all equally reflect the severity of the stenosis and there is no clear advantage in using one parameter rather than the other. In contrast, if cardiac index is decreased, such as might occur in patients with severe aortic stenosis and LV dysfunction (patients 4, 5, and 6), the only common denominator is the indexed EOA, whereas the values for pressure gradients and valve RES are greatly decreased compared with the previous situation (patients 1, 2, and 3). For instance, patients 2 and 5 have similar valve EOAs and body surface areas and therefore similar stenosis severity. However, the gradient and valve RES are much lower in patient 5 who has a low cardiac output, and both values tend to underestimate the severity of the stenosis. This example illustrates that, because of its flow dependence, valve RES is of very limited value for interindividual comparisons of stenosis severity. In this context, much of the justification for the use of resistance is based on the study by Cannon et al¹¹ and, in particular, on their observation of a small group of patients whose EOA values tended to exaggerate stenosis severity versus resistance. However, these EOA values were not indexed for body surface area and a possible explanation for this discrepancy could be that these patients had a small body surface area, in which case indexed EOAs would have provided better assessments and allowed more precise interindividual comparisons.

Several in vitro and in vivo studies demonstrate that the EOA of native or prosthetic valves can increase with increasing flow rates, and in varying degrees depending on valve geometry and compliance.^{1-9,18,27-29} It becomes clear from the results of the present study that none of the resting parameters, whether EOA, indexed EOA, gradient, or valve RES, can predict the behavior of an individual

valve in response to an increase in flow. Accordingly, the need to perform dobutamine or exercise stress tests in certain clinical situations is not obviated. It also remains to be determined if the use of resistance in these circumstances has advantages over simply calculating EOA and gradient.

Acknowledgment: We thank Jean Jobin, PhD, for assistance in the design of the exercise protocol, Louise Côté, RN, and Jacinthe Aubé, RN, for the recruitment of patients, and Isabelle Laforest, MS, Jocelyn Beauchemin, RT, and Martin Noël, BSc, for their technical assistance.

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