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Effects of Dobutamine on Doppler Echocardiographic Indexes of Aortic Stenosis

JAVIER BERMEJO, MD, MIGUEL A. GARCÍA-FERNÁNDEZ, MD, ESTEBAN G. TORRECILLA, MD, HÉCTOR BUENO, MD, M. MAR MORENO, MD, DANIEL SAN ROMÁN, MD, JUAN LUIS DELCÁN, MD

Madrid, Spain

Objectives. **This study sought to assess the diagnostic implications of the flow dependence of Doppler echocardiographic indexes of aortic valve stenosis.**

Background. **Although valve area has been shown to change with alterations in flow rate, the diagnostic consequences of this phenomenon remain unknown. Valve resistance has been suggested as a more stable index for evaluating aortic stenosis.**

Methods. **A low dose dobutamine protocol was performed in 35 patients with aortic stenosis. Hemodynamic indexes were obtained by Doppler echocardiography at baseline and at each dobutamine dose.**

Results. **As a result of the shortening of the systolic ejection period, flow increased from (mean ± SD) 164 ± 48 to 229 ± 102 ml/s ($p < 0.0001$). At peak flow, valve area increased by 28% (from 0.5 ± 0.2 to 0.6 ± 0.3 cm^2, $p < 0.0001$), whereas valve resistance decreased by 4% (from 498 ± 252 to 459 ± 222 dynes·s·cm^{-5}, $p = 0.04$). This observed change in resistance was smaller than that for valve area ($p < 0.01$). The flow dependence of valve area varied among individual patients ($p < 0.0001$). Multivariate analysis identified calcific degenerative etiology (beta 0.29, $p = 0.002$), left ventricular velocity of fiber shortening (beta 0.22, $p = 0.01$), baseline flow (beta −0.28, $p = 0.04$) and amount of flow increase induced by dobutamine (beta 0.90, $p < 0.0001$) as factors related to valve area flow dependence.**

Conclusions. **Although all Doppler echocardiographic indexes of aortic stenosis are affected by flow, valve resistance is more stable than valve area under dobutamine-induced hemodynamic changes. Baseline valve area may be unreliable in patients with calcific degenerative aortic stenosis and low output states.**

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Valve area is currently accepted as the most useful index for assessing the hemodynamic burden imposed by a stenotic cardiac valve (1). However, use of the Gorlin method to calculate valve area may be unreliable because valve area is known to change with alterations in flow (2–7). Moreover, valve area derived by Doppler echocardiography has also been reported to be flow dependent (7–9). These findings have stressed the possibility of misdiagnosing aortic stenosis when flow rate is low, a phenomenon that has been severally designated as *flow-dependent, relative* or *pseudo* severe aortic stenosis (9–11). In such cases, the pharmacologic increase of flow has been recommended (9,10) to correctly assess disease severity, and preliminary attempts to base clinical decisions on these protocols have been reported (9,12). However, several issues remain to be defined: 1) Flow dependence of aortic valve area derived by Doppler echocardiography has been confirmed only in selected groups of patients with aortic stenosis. 2) It remains to be elucidated whether valve area flow dependence occurs mainly at low flow states or at all ranges of volumetric flow rate. 3) Differences in flow dependence among the different varieties of the disease have not been assessed. Aortic valve resistance has been proposed (13,14) as an alternative index of aortic stenosis because it is expected to remain more stable under changing hemodynamic conditions.

The present study was therefore designed to study the effects of dobutamine-induced flow augmentation on Doppler echocardiographic indexes of aortic valve stenosis in an unselected group of patients with this disease.

Methods

The study protocol was approved by our institutional review board. Written informed consent was obtained from all patients.

Patients. The study group originally included 57 consecutive adult patients referred to our echocardiography laboratory, in whom aortic valve stenosis was diagnosed on routine ultrasound evaluation (aortic velocity ≥2.5 m/s assessed by continuous wave Doppler). Only four exclusion criteria were established: 1) a suboptimal echocardiographic window (n =

From the Department of Cardiology, Hospital General Universitario Gregorio Marañón, Madrid, Spain. This study was presented in part at the 68th Scientific Sessions of the American Heart Association, Anaheim, California, November 1995 and at the XVIIth Congress of the European Society of Cardiology, Amsterdam, The Netherlands, August 1995.

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Address for correspondence: Dr. Javier Bermejo, Laboratory of Echocardiography, Department of Cardiology, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo 46. 28007 Madrid, Spain.

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Abbreviations and Acronyms

CI = confidence interval
EF = ejection fraction
$\overline{Q}$ = mean systolic transvalvular volume flow rate
V_{cf} = left ventricular heart rate-corrected velocity of circumferential fiber shortening

2); 2) New York Heart Association functional class IV (n = 5); 3) the presence of major ventricular arrhythmias (n = 1); and 4) atrial fibrillation (n = 12). Two patients declined to participate in the study; therefore, the remaining 35 patients form the basis for this report.

To evaluate the factors related to valve area changes, a subgroup of 25 patients with isolated aortic stenosis were selected according to the absence of 1) segmental wall motion abnormalities (either at baseline or dobutamine induced), 2) significant mitral stenosis, and 3) mitral or aortic regurgitation. Clinical characteristics are shown in Table 1.

Study protocol. A complete Doppler echocardiographic examination was performed using a phased-array ultrasound device (Hewlett-Packard Sonos 1500 or 2500) with 2.5/2.0-MHz duplex and 1.9-MHz (Pedoff) transducers. Best quality frames and cardiac cine loops were stored on a digital magneto-optical disk for subsequent analysis. Left ventricular outflow tract diameter was measured in the parasternal long-axis view at the point of insertion of the sigmoid valves. To record left ventricular outflow velocity, a 5-mm long pulsed Doppler sample volume was located 1 cm proximal to the valve plane in the apical view and then advanced until spectral broadening was detected. Special care was taken to retain sample volume location throughout the complete protocol. The aortic jet was interrogated with continuous wave Doppler from multiple ultrasound views, and the location that showed maximal velocity was marked on the patient's chest wall. High pass filters were set at 400 Hz for pulsed and at maximum for continuous wave Doppler; filters remained unchanged throughout the complete protocol.

Table 1. Clinical Data for All Patients and Subgroup With Isolated Aortic Stenosis

	All Patients (n = 35)	Isolated AS (n = 25)
Age (yr)*	71 ± 14	71 ± 15
Range	31–87	50–87
Male/female (n)	16/19	9/16
Etiology of AS [n (%)]		
Degenerative calcific	25 (71)	19 (76)
Rheumatic	7 (20)	5 (20)
Bicuspid	3 (9)	1 (4)
Symptoms [n (%)]		
None	11 (31)	9 (36)
Angina	9 (26)	5 (20)
Exertional dyspnea	10 (29)	8 (32)
Syncope	2 (6)	1 (4)
Congestive heart failure	7 (20)	5 (20)

*Median ± interquartile amplitude. AS = aortic stenosis.

After the baseline study, a low dose dobutamine infusion protocol was begun at 5 μg/kg body weight per min up to 20 μg/kg per min, titrated upward at steps of 5 μg/kg per min every 5 min. The dobutamine infusion was ended when the maximal dose or 85% of the maximal theoretic heart rate was reached; when patients developed dyspnea, angina, dizziness or hypotension; or when changes in left ventricular segmental contractility were detected. Atenolol (2.5 mg intravenously) was administrated to all patients who presented symptoms during dobutamine infusion. Spectral displays of left ventricular outflow tract and aortic stenosis jet velocity were obtained within the last 2 min of each dose. When necessary, progression to the next step was delayed until Doppler recordings were considered optimal. Blood pressure and the electrocardiogram were monitored noninvasively.

Data analysis. Two-dimensional and Doppler echocardiographic images were evaluated off-line by a single experienced echocardiographer (J.B.), using built-in software, calipers and the trackball of the echocardiographic equipment used for image acquisition. End-diastolic and end-systolic endocardial areas (LVA_d and LVA_s, respectively) were traced from two-dimensional parasternal short-axis views. Heart rate-corrected mean velocity of circumferential fiber shortening (V_{cf}) was computed from these areas such that $V_{cf} = (LVA_d - LVA_s)/(LVA_d \cdot SEP/\sqrt{RR})$, where SEP is the systolic ejection period, measured as the time between aortic valve opening and closure echoes in the aortic Doppler recording. Left ventricular volumes, ejection fraction and mass were calculated by the biplane method of disks (15). Left ventricular outflow tract cross-sectional area (CSA_{LVOT}) was derived from its diameter assuming a circular shape. Three to five consecutive Doppler curves of left ventricular outflow tract and aortic velocities were traced in the basal state and for each dobutamine dose. Systolic time-velocity integrals (TVI_{LVOT}, TVI_{Ao}) were then averaged. Stroke volume (SV) was calculated as $TVI_{LVOT} \cdot CSA_{LVOT}$ and mean systolic transvalvular volume flow rate ($\overline{Q}$) as SV/SEP (16). Mean transaortic pressure gradient ($\overline{Grad}$) was obtained using the simplified Bernoulli equation. Mean aortic valve resistance (AVR) and aortic valve area (AVA) were calculated, respectively, as $AVR = \overline{Grad} \cdot 1.333/\overline{Q}$ and $AVA = TVI_{LVOT} \cdot CSA_{LVOT}/TVI_{Ao}$ (17). To assess intraobserver and interobserver variability, 20 patients were randomly selected. Their cardiac cine loops of left ventricular outflow diameter and baseline Doppler tracings were then remeasured.

The etiology of aortic stenosis was assumed to be rheumatic when coexisting characteristic mitral valve disease was observed by two-dimensional transthorathic echocardiography. A congenital bicuspid valve was diagnosed in three patients and confirmed by identification of only two leaflets and two commissures by multiplane transesophageal echocardiographic examination; valve calcification was absent. All other cases were considered to be of the calcific degenerative type.

Table 2. Absolute and Relative Variability of Indexes of Aortic Stenosis Derived by Doppler Echocardiography

	Intraobserver Variability (mean ± SD)	Interobserver Variability (mean ± SD)
$\overline{Grad}$ (mm Hg)	5 ± 4	8 ± 4
$\overline{Grad}$ (%)	9 ± 6	14 ± 7
TVI_{LVOT}/TVI_{Ao} (%)	5 ± 6	5 ± 6
AVA (cm^2)	0.07 ± 0.07	0.08 ± 0.09
AVA (%)	14 ± 11	18 ± 16
AVR ($dynes \cdot s \cdot cm^{-5}$)	88 ± 66	100 ± 92
AVR (%)	18 ± 12	21 ± 17

AVA = aortic valve area; AVR = aortic valve resistance; $\overline{Grad}$ = mean systolic transaortic pressure gradient; TVI_{LVOT} and TVI_{Ao} = Time-velocity integrals of left ventricular outflow tract and aorta, respectively.

Table 3. Baseline Echocardiographic Data for All Patients and Subgroup With Isolated Aortic Stenosis

	All Patients (n = 35)	Isolated AS (n = 25)
AVA (cm^2)	0.5 ± 0.2 (0.2–1.3)	0.5 ± 0.2 (0.2–1.1)
AVR ($dynes \cdot s \cdot cm^{-5}$)	498 ± 252 (80–1241)	518 ± 262 (114–1241)
$\overline{Grad}$ (mm Hg)	55 ± 21 (14–100)	58 ± 22 (20–100)
LVEDVI (ml/m^2)	63 ± 28 (24–170)	59 ± 22 (24–109)
V_{cf} (s^{-1})	1.3 ± 0.6 (0.2–2.6)	1.4 ± 0.6 (0.5–2.5)
Ejection fraction	0.6 ± 0.2 (0.2–0.8)	0.6 ± 0.1 (0.2–0.8)
LVMI (g/m^2)	154 ± 62 (58–401)	160 ± 71 (58–402)

Data presented are mean value ± SD (range). V_{cf} = left ventricular heart rate-corrected mean velocity of circumferential fiber shortening; LVEDVI = left ventricular end-diastolic volume index; LVMI = left ventricular mass index; other abbreviations as in Table 2.

Statistical analysis. Results are presented as mean value ± SD, unless otherwise indicated. The regression equation of valve resistance was obtained from pooled values from all dobutamine doses using Newton-Raphson nonlinear fitting (see Appendix). Absolute and relative variabilities of aortic stenosis indexes were obtained as previously recommended (18) (Table 2).

Hemodynamic changes were assessed by one-way analysis of variance accounting for repeated measures (multivariate analysis of variance). Baseline indexes of aortic stenosis were compared with those obtained at the dose of peak $\overline{Q}$ for each patient, using Spearman's correlation coefficient and the paired *t* test. Absolute percent of these index changes were compared by factorial analysis of variance followed by the Tukey-Kramer test. Interindividual differences were assessed by least-squares linear regression analysis accounting for repeated measures and different slopes where the dependent variable was transformed to its natural logarithm to stabilize variance. The association of clinical and hemodynamic factors with valve area enlargement was tested using Spearman's correlation coefficient. Etiology of aortic stenosis was coded as a dichotomous variable, grouping calcific variety as one group and rheumatic and congenital as the other. The same variables except clinical status were then screened by multivariate analysis. The multiple linear regression model was selected using the "all subsets regression" procedure focused on the best Mallow's conditional mean squared error of production criteria (C_p index) (19). Because of the small sample size, special care was taken to verify that data met the assumptions for multiple regression (19). All statistical analyses were performed using the JMP statistical software program (Version 3.0., SAS Institute Inc.), except all subsets regression (BMDP Version PC90, BMDP Statistical Software Inc.) and multivariate analysis of variance (SPSS Version 4.0, SPSS Inc.). A p value <0.05 was considered significant.

Results

Clinical response to dobutamine protocol. Baseline echocardiographic data are shown in Table 3. No major complications occurred with dobutamine infusion. Four patients (9%) experienced angina, which disappeared <10 min after discontinuation of dobutamine and the administration of atenolol; all four complained of exercise angina. Coronary angiography revealed multivessel disease in two of these patients but no lesions in the other two. One patient developed an asymptomatic atrial tachycardia that reverted to sinus rhythm after atenolol administration, and one had asymptomatic hypotension (decrease of 22 mm Hg in systolic arterial pressure). End-systolic acceleration at the left ventricular outflow tract took place in three patients, leading to discontinuation of dobutamine before aliasing of the Doppler signal occurred.

Hemodynamic changes induced by dobutamine. As shown in Figure 1, a strong correlation between valve area and resistance was obtained for a given transaortic gradient (r^2 = 0.99). Figure 2 summarizes the hemodynamic changes induced by dobutamine. Cardiac output increased from 3.6 ± 1.0 liters/min at baseline to 5.5 ± 2.2 liters/min at peak dobutamine dose ($p < 0.0001$ for all dose comparisons). However, this change resulted from an increase in heart rate because stroke volume remained constant ($p = 0.06$). Shortening of the systolic ejection period resulted in a mean systolic transvalvular flow rate increase, from 164 ± 48 to 229 ± 103 ml/s ($p < 0.0001$). Transvalvular flow rate correlated with the dobutamine dose infused at that moment ($r^2 = 0.93$, $p < 0.0001$), but the response of flow to dobutamine was different among individual patients ($p < 0.0001$ and $p = 0.001$ for between subjects and between subject-dobutamine dose effects, respectively).

Changes in indexes of aortic stenosis induced by dobutamine. Figure 3 shows the changes in aortic stenosis indexes induced by dobutamine. Both mean transaortic gradient and aortic valve area increased significantly with dobutamine infusion ($p < 0.0001$ for both tests). A mean increase of 40% in pressure gradient was observed at the dobutamine-induced maximal flow (from 55 ± 21 to 75 ± 26 mm Hg, $p < 0.0001$, 95% confidence interval [CI] 15 to 25). Compared in the same way, valve area increased by 28% (from 0.5 ± 0.2 to 0.6 ± 0.3 cm^2, $p < 0.0001$, 95% CI 0.1 to 0.2). Multiple-dose comparison of valve resistance disclosed no change during

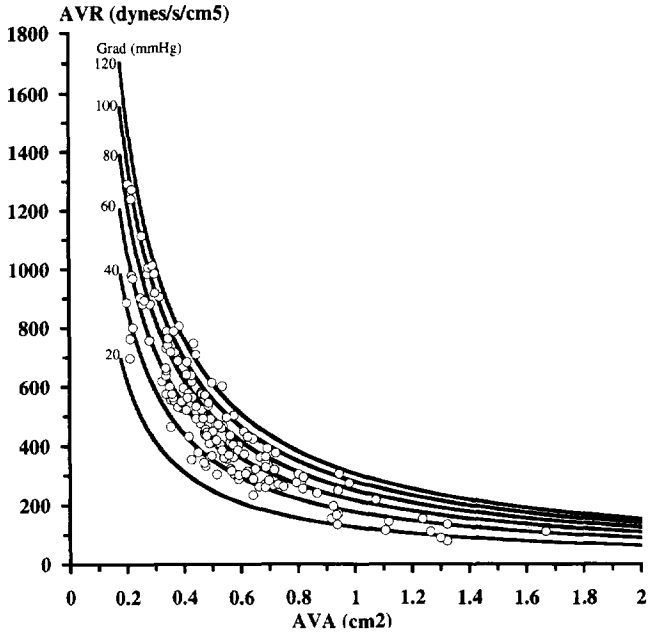

Figure 1. Scatterplot of aortic valve area (AVA) and aortic valve resistance (AVR) obtained from pooled values from all dobutamine doses. The regression curves obtained for aortic valve area and aortic valve resistance are shown for different values of mean transaortic pressure gradient (Grad) and were obtained from the relation AVR = $28\sqrt{\text{Grad}}/\text{AVA}$. See Appendix for details.

dobutamine infusion (p = 0.6) (Fig. 3). However, a small decrease in valve resistance was observed at the dose of peak flow (mean 4%; from 498 ± 252 to 459 ± 222 dynes·s·cm^{-5}, p = 0.04, 95% CI 2 to 76). Changes in the group with isolated aortic stenosis were similar: Gradient increased by 42% (from 57 ± 22 to 79 ± 25 mm Hg, p < 0.0001, 95% CI 16 to 26) and valve area by 31% (from 0.4 ± 0.2 to 0.6 ± 0.3 cm^2, p < 0.0001, 95% CI 0.1 to 0.2), but resistance did not change significantly (from 518 ± 263 to 476 ± 236 dynes·s·cm^{-5}, p = 0.08).

Values at baseline and at maximal flow closely correlated, both for valve area and resistance (rho 0.85 and 0.87, respectively). The mean absolute percent change in valve resistance observed between baseline and peak flow values was smaller than that for mean gradient and valve area (p < 0.0001 and p < 0.01, respectively); no difference was observed between the latter two indexes (p > 0.05) (Fig. 4).

Two patients showed a small valve area (≤0.7 cm^2) and a low gradient (≤35 mm Hg) at baseline study. One patient had associated chronic arterial hypertension and was asymptomatic; although her left ventricular function was not impaired (ejection fraction [EF] 0.7, V_{cf} = 1.4/s), both cardiac index and transvalvular flow were low (cardiac index 1.7 liters/min per m^2; $\overline{Q}$ = 190 ml/s). Dobutamine infusion increased flow by 85%, enlarging valve area by 60% (from 0.4 to 0.7 cm^2) and decreasing resistance by 26% (from 354 to 261 dynes·s·cm^{-5}). The other patient had heart failure and left ventricular dysfunction (EF = 0.3; V_{cf} = 0.8/s; cardiac index 0.9 liters/min per m^2; $\overline{Q}$= 59 ml/s). Dobutamine up to 20 μg/kg per min induced no relevant change in either flow (6%) or valve area (6%; from 0.2 to 0.2 cm^2); resistance increased by 15% (from 697 to 801 dynes·s·cm^{-5}).

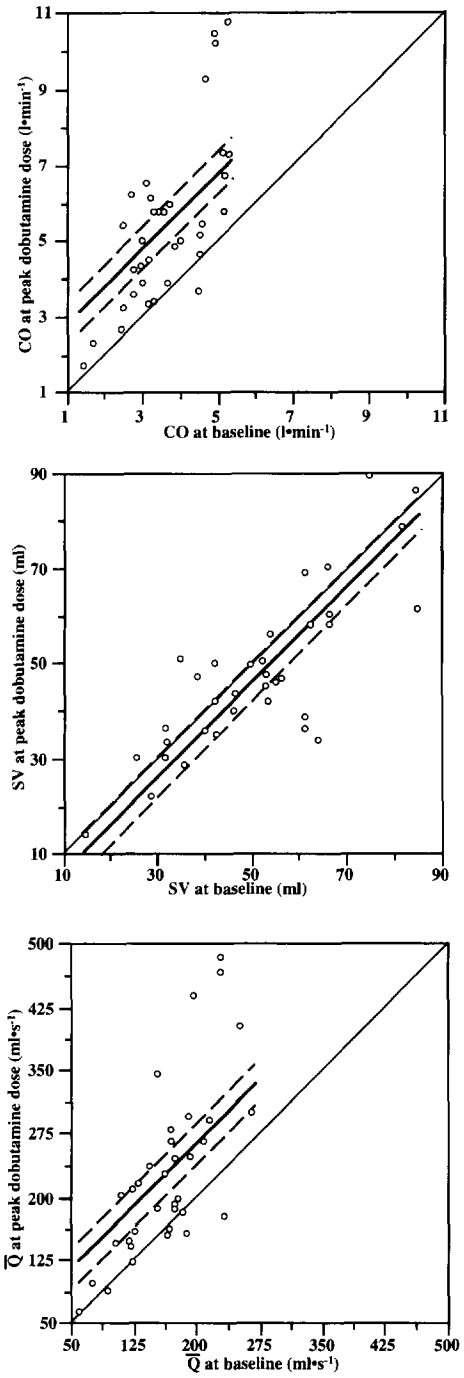

Figure 2. Scatterplot of hemodynamic variables at baseline and peak dobutamine dose. Values above the identity line (**thin line**) represent an increase in the hemodynamic variable from baseline to peak dobutamine dose; values below this line represent a decrease. The **thick line** has the same slope as the identity line but is displaced by the difference in the mean values; **dashed lines** represent the 95% CI for this mean difference. The lack of increase in stroke volume at peak dobutamine dose is represented by the inclusion of the identity line within the dashed lines. CO = cardiac output; $\overline{Q}$ = mean systolic transvalvular flow rate; SV = stroke volume.

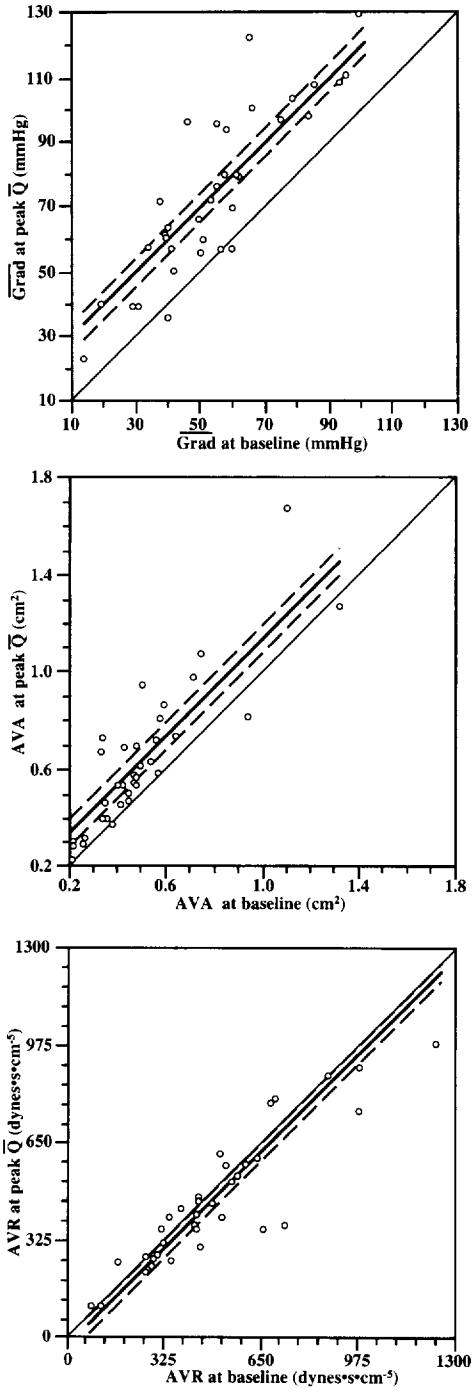

Figure 3. Scatterplot of hemodynamic indexes of aortic stenosis at baseline and at peak mean systolic transvalvular flow rate. Interindividual differences in the amount of change induced by dobutamine in a specific index (i.e., aortic valve resistance) can be observed because patients with similar values at baseline disclose a wide range of values at peak Q. Grad = mean systolic transaortic pressure gradient; symbols and other abbreviations as in Figures 1 and 2.

Interindividual variability of valve area flow dependence. A strong correlation was observed between aortic valve area and transvalvular flow rate at each dobutamine dose in the same patient ($r^2 = 0.98$, $p < 0.0001$); however, the level of dependence varied among patients ($p < 0.0001$ and $p = 0.006$ for the between patients and between patient·flow rate effects, respectively).

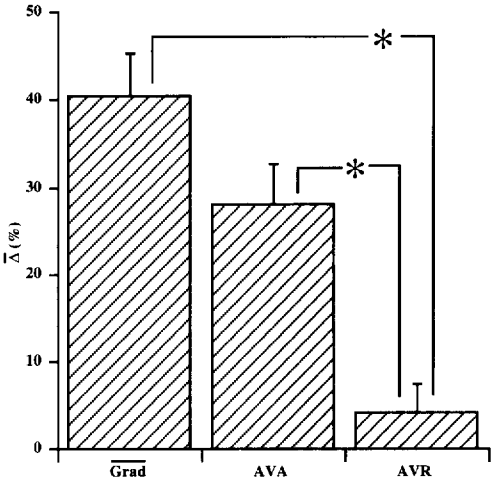

Figure 4. Mean (SE) absolute percent changes [$\bar{\Delta}$(%)] in indexes of aortic stenosis observed from baseline to the dobutamine dose producing maximal mean systolic transvalvular flow rate. *$p < 0.01$ for Tukey-Kramer comparison test. Abbreviations as in Figure 1.

Factors related to aortic valve area increase. Variables related to valve area increase are shown in Table 4. By multivariate analysis, the amount of flow augmentation induced by dobutamine was the most important factor related to orifice enlargement (beta 0.90), followed by calcific etiology of the disease (beta 0.29), V_{cf} (beta 0.22) and baseline flow rate (beta −0.28).

Discussion

Flow dependence of aortic valve area. Flow dependence of aortic valve area has been reported in several in vitro (20), animal (7) and clinical studies, both for the Gorlin (2–6) and Doppler echocardiographic (5,8,9) methods of estimating valve area. In the largest Doppler echocardiographic study reported, Burwash et al. (8) calculated aortic valve area at baseline and after maximal treadmill exercise in asymptomatic patients with aortic stenosis. They reported a mean valve area enlargement of 14%, parallel to a 24% increase in transvalvular flow. The present study demonstrated that dobutamine may also increase continuity equation-derived valve area in unselected patients. By increasing heart rate and shortening the ejection period, dobutamine increased transvalvular flow and induced a 28% increase in valve area. Two small clinical studies (5,9) have assessed the effects of dobutamine on Doppler echocardiographic valve area, and pooled data from these two studies (total 24 patients) reveal changes in valve area consistent with our findings.

The present study showed that valve area may increase with no modification of stroke volume. The basis for this finding is that, rather than volume, the forces that promote valve aperture are mediated by flow rate (volume of blood per second of

Table 4. Univariate and Multivariate Variables Related to Absolute Valve Area Increase in Subgroup With Isolated Aortic Stenosis*

	Univariate Analysis		Multivariate Analysis		
	Rho	p Value	Coefficient (b)	Standardized Coefficient (beta)	p Value
Symptomatic status					
Dyspnea, angina or syncope	0.3	0.1			
Etiology of AS					
Calcific degenerative	0.03	0.9	0.1	0.29	0.002
Indexes of LV function					
Ejection fraction	0.3	0.02			
V_{cf}	0.5	0.11	0.06	0.22	0.01
LV mass index	−0.5	0.01			
Hemodynamic factors					
Baseline cardiac output	0.2	0.3			
Baseline $\overline{Q}$	0.2	0.3	−0.0008	−0.28	0.04
Baseline AVA	0.3	0.1	0.13	0.19	0.2
Baseline AVR	−0.4	0.07			
Baseline $\overline{Grad}$	−0.2	0.33			
Dobutamine-induced $\Delta\overline{Q}$	0.9	<0.0001	0.002	0.90	<0.0001

*Multiple regression model selected by "all subsets regression" procedure based on the best Mallow's conditional mean squared error of prediction (Cp index) (r^2 = 0.91, SE 0.05 cm^2, $p < 0.0001$ for the whole model). LV = left ventricular; $\overline{Q}$ = mean systolic transvalvular volume flow rate; Δ = change in; other abbreviations as in Tables 1 to 3.

ejection). As observed in our study, pharmacologic interventions were able to increase flow rate and induce aortic enlargement only by shortening ejection time. Exercise, by the same mechanism, is known to increase valve area even though it reduces stroke volume in patients with aortic stenosis (8,21–23). Shortening of the ejection period is reflected by an increase in continuity equation-based valve area because the aortic integral (denominator) is reduced, with no change in stroke volume (numerator).

Comprehensive assessment of the hemodynamic principles on which the Gorlin and continuity equation methods are based has led to the interpretation of the flow-mediated changes in valve area as variations in the anatomic orifice and not as artifacts of the computation formulas (8,24). Hence, it is the degree of true obstruction that seems to be flow dependent. However, valve area obtained by planimetry of the aortic orifice by means of transesophageal echocardiography has been shown (25) to remain constant under hemodynamic changes. We believe that a possible explanation for this discrepancy may be due to conceptual differences between anatomic and effective areas. *Anatomic valve area*, as assessed by planimetry, accounts for the maximal mid–end-systolic area at a precise moment in the heart cycle (26). *Effective valve area*, as assessed by indirect hemodynamic methods, accounts for pansystolic functional area, averaged throughout the complete ejection period (27,28). Thus, dobutamine-induced changes in effective area may be due to a change in the timing of maximal leaflet opening because leaflet inertia may be overcome earlier when flow is augmented.

Our study corroborates the strong linear correlation between transvalvular flow and valve area in an individual patient, which was demonstrated invasively in a canine model of chronic aortic stenosis (7). Remarkably, the grade of flow dependence varied from one patient to another (Fig. 3), which demonstrates the influence of individual factors on the orifice enlargement reserve. Multivariate analysis identified baseline flow, left ventricular function and type of disease as the factors related to the increase in valve area once the effect of augmentation was considered. By univariate analysis, no single variable was able to predict the increase in valve area. This result was probably due to the interindividual differences observed in the flow response to dobutamine.

The appearance of an association between area enlargement and calcific degenerative etiology of aortic valve stenosis suggests a role for the physical characteristics of the valve in modulating valve aperture. Because commisural fusion is absent, leaflet inertia is one of the principal mechanisms of orifice reduction in calcific degenerative aortic stenosis; therefore, this type of disease may be especially prone to flow variations (11,29–31).

The increase in valve area was inversely related to baseline flow, a finding in accordance with the concept of flow-dependent aortic stenosis. In vitro video recordings of the opening of aortic valves have demonstrated (20) that valve orifice is flow dependent mainly at flow rates <3 liters/min. However, Burwash et al. (8) observed no difference in orifice enlargement between patients with and without depressed cardiac output. As formerly stated, this discrepancy may be due to the type of analysis performed because univariate comparisons cannot account for the confounding effect of flow response to dobutamine. A direct correlation was also observed between the increase in valve area and left ventricular velocity of circumferential fiber shortening. Because this index is strongly affected by systolic wall stress in aortic stenosis, such

an association could be due to the effect of valve stiffness on ventricular afterload (32).

Flow dependence of valve resistance. Valve resistance was more stable than area when flow was increased, a finding consistent with previous observations (33,34). Because of the hydraulic models from which each index is derived, it is not possible for valve area and resistance to remain constant at a time (see Appendix). Area is based on Torricelli's principle of laminar flow through a flat orifice in which gradient is proportional to the square of flow [$\overline{Grad} = f(\overline{Q}^2)$]. However, resistance assumes a linear relation between these variables [$\overline{Grad} = f(\overline{Q})$]. Recent investigations (35) have further proposed a quadratic flow–gradient relation [$\overline{Grad} = f(\overline{Q}^2 + \overline{Q})$]. The demonstration of flow-mediated orifice variability suggests that the hemodynamic load imposed by aortic valve stenosis may be inadequately evaluated if patients are studied only at baseline; hence, searching for a flow-independent index of severity would be inappropriate.

Other than increasing transaortic gradient, the main hemodynamic effect of dobutamine was to shorten the systolic ejection period. This variable constitutes a term of the formula for valve resistance and by compensating the increase in gradient, may explain why resistance remained fairly stable. To prove the flow stability of this index, corroboration of our results by interventional methods that increase flow without modifying the ejection period would be necessary.

Study limitations. Calculation of hemodynamic indexes by Doppler echocardiography is known to be subject to several methodologic limitations, such as underestimation of stenotic jet velocity and overestimation of proximal velocity. The following four precautions were taken to minimize these errors: 1) The study was designed to calculate orifice enlargement as the change from baseline to dobutamine-induced maximal flow rate rather than dobutamine-induced maximal area. 2) The position of the Doppler transducer and sample volume were maintained throughout the protocol. 3) Dobutamine dose increase was delayed until Doppler recordings were considered optimal. 4) Only the highest quality signals were selected for analysis. However, because valve area and transvalvular flow rate were derived from the same Doppler echocardiographic data, their correlation may have been overestimated.

The observed change in valve area may seem nonsignificant because it is almost within the confidence interval of the variability of the method (Table 2). However, most such variability is due to measurement of the outflow tract diameter. This variable is assumed to be anatomically fixed and therefore unrelated to the effect of flow. Because only measurement of velocity curves and systolic ejection period was repeated for each dose, variability of Doppler echocardiographic indexes in the same patient was considerably reduced (Table 2).

Clinical implications. The mean change observed for valve area was 20% and may seem clinically irrelevant. Yet, the observation of an inverse correlation between baseline flow and orifice enlargement emphasizes the importance of such a finding because patients with aortic stenosis and low cardiac output are known to have a poor prognosis during and after valve replacement (36,37). Consequently, correct assessment of the severity of stenosis is mandatory (38). The present study suggests that in these patients, a flow-dependent underestimation of valve area is likely. Initial experience with clinical decisions based on dobutamine protocols is satisfactory (9,12,39). Whether valve resistance or flow-mediated changes in hemodynamic indexes can provide new, clinically relevant information in terms of outcome and timing of valve replacement remains unknown. Longitudinal studies to evaluate the superiority of these alternative assessments of aortic stenosis are therefore warranted.

Appendix

Derivation of Aortic Valve Area–Valve Resistance Relation

On the basis of the definition formulas of both aortic valve area (AVA) and aortic valve resistance (AVR)—$AVA = Q/k\sqrt{\overline{Grad}}$ and $AVR = \overline{Grad}/\overline{Q} \cdot 1.33$—a new constant may be substituted for 1.33/k such that $AVR = a\sqrt{\overline{Grad}}/AVA \approx 28\ \sqrt{\overline{Grad}}/AVA$, where the value $a \approx 28$ is obtained by nonlinear regression analysis of our pooled data (asymptotic 95% CI 27.81 to 28.01, $n = 175$, $r^2 = 0.99$). By this equation, valve resistance can be accurately calculated from area and gradient without knowledge of the systolic ejection period. The equation also demonstrates why area must increase as gradient increases for resistance to remain constant.

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