

# Usefulness of Dobutamine Echocardiography in Distinguishing Severe from Nonsevere Valvular Aortic Stenosis in Patients with Depressed Left Ventricular Function and Low Transvalvular Gradients

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In adults with aortic stenosis (AS), valve replacement is recommended if symptoms are accompanied by severely reduced aortic orifice area.<sup>1-5</sup> In such patients, valve replacement improves symptoms and life expectancy, even in the setting of left ventricular (LV) dysfunction. LV dysfunction in severe AS is usually due to afterload mismatch, to the extent that valve replacement relieves the afterload excess imposed by the stenotic valve and improves LV performance.<sup>6,7</sup> However, a subset of patients with severe AS, LV dysfunction, and low transvalvular gradients have a high operative mortality.<sup>7-9</sup> Accurate assessment of aortic valve area in such patients is difficult<sup>10</sup> because calculated valve area is directly proportional to cardiac output<sup>11-13</sup> and the Gorlin constant varies at low flow states.<sup>14-16</sup> Cannon et al<sup>17</sup> showed that some patients with LV dysfunction and low mean gradients have Gorlin valve areas indicating critical AS when the valve is only moderately diseased at surgery. This study was performed to determine whether dobutamine echocardiography, which enables aortic valve area calculation at 2 different flow conditions (baseline and dobutamine), could distinguish between severe fixed AS and flow-dependent (relative) AS in patients with LV dysfunction and low mean gradients.

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We studied 24 consecutive patients recruited for symptomatic severe native valve AS (aortic valve area  $\leq 0.5$  cm<sup>2</sup>/m<sup>2</sup>),<sup>18</sup> mean transvalvular gradients  $\leq 30$  mm Hg,<sup>9</sup> and LV dysfunction (LV ejection fraction  $\leq 0.45$ ). Patients were excluded if they were too ill to participate ( $n = 3$ ), had technically difficult echocardiograms ( $n = 2$ ), or atrial fibrillation ( $n = 1$ ). Thus, 18 patients (age  $70 \pm 9$  years) completed the study. Significant coronary artery disease ( $\geq 50\%$  stenosis) was present in 8 (44%) (Table I). No patient had more than mild aortic regurgitation.

Patients were studied using either a 2.5/2.0 MHz (Hewlett-Packard Sonos 1500) or a 3.25/2.5 MHz (Vingmed CFM750) transducer. Baseline 2-dimensional echocardiographic images were obtained in standard parasternal and apical views. Pulsed Doppler spectra of LV outflow tract velocities were recorded from the apical view with the sample volume placed just proximal to the aortic annulus to avoid flow acceleration artifact. Continuous-wave Doppler spectra were sampled from api-

cal, suprasternal, and right parasternal views using spectral and audio signals to identify the maximal aortic flow velocity.

Heart rate, blood pressure, rhythm, and wall motion were monitored throughout the procedure. Intravenous dobutamine was started at 5  $\mu$ g/kg/min and increased by 5  $\mu$ g/kg/min every 3 minutes until a maximal dose of 20  $\mu$ g/kg/min was obtained. The protocol was stopped at lower doses for wall motion abnormalities, hypotension, or significant adverse side effects. The last stage was continued for 6 minutes to acquire final echocardiographic and Doppler data, which were obtained from the same transducer position as at baseline.

LV ejection fraction was assessed by biplane Simpson's rule at baseline and after dobutamine. Regional wall motion was assessed on a quad screen display using the 16-segment model in which each segment was graded as 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic.<sup>19</sup> Wall motion score was calculated at baseline and peak dobutamine as described previously.<sup>19,20</sup> LV contractile reserve was defined as  $\geq 20\%$  improvement in wall motion score, a value that represents the 95% confidence limit for a change in wall motion score in our laboratory.<sup>20</sup>

Continuous-wave Doppler spectra were traced to assess peak velocity, mean gradient, and velocity-time integral. The 3 highest velocity beats were averaged; postextrasystolic beats were avoided. LV outflow tract diameter was measured in the long-axis view and its cross-sectional area calculated assuming a circle. Aortic valve area was calculated by the continuity equation as the product of the area and velocity-time integrals of the LV outflow tract divided by the velocity-time integral of the AS jet.<sup>21,22</sup> In our laboratory, the standard error of the estimate for repeated measurements of aortic valve area in a patient is 0.15 cm<sup>2</sup>. Therefore, we considered a valve area increase of 0.3 cm<sup>2</sup> to be significant at the 95% confidence interval.<sup>18</sup>

Aortic valve resistance was calculated as  $(1.33)(\text{MPG})(\text{SEP})/\text{SV}$ ,<sup>23,24</sup> where MPG is the mean pressure gradient by continuous-wave Doppler, SEP is the systolic ejection period, and SV is the stroke volume determined from the product of LV outflow tract area and velocity-time integrals. The constant 1.33 is a correction factor used to express valve resistance in dynes.s.cm<sup>-5</sup>.

Patients were grouped according to the presence (group I) or absence (group II) of contractile reserve. Group I was further stratified into those without a significant change in aortic valve area (group IA) or those in whom aortic valve area increased by  $\geq 0.3$  cm<sup>2</sup> with dobutamine (group IB). Repeated-measures analysis of variance was used to assess between- and within-group

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**TABLE I** Clinical and Hemodynamic Variables

Patient	Age (yr) & Sex	Group	CAD*	RWMS	LVEF (%)	LVED (cm)	LVes (cm)	SWT (cm)	PWT (cm)	LA (cm)	LVP (mm Hg)
1	56 M	IA	0	2.7	20	6.4	5.9	1.2	1.2	4.5	116/30
2	70 M	IA	3	2.0	33	6.8	5.9	1.1	1.1	4.1	140/34
3	69 M	IA	—	1.88	24	5.9	4.3	1.1	1.2	3.9	—
4	59 F	IA	2	2.69	26	6.0	5.7	1.0	0.9	3.7	147/13
5	66 M	IA	1	2.38	32	6.7	6.0	1.5	1.5	4.1	130/32
6	68 M	IA	0	2.7	30	5.6	5.2	1.4	1.3	4.6	132/24
7	71 F	IA	—	2.94	26	5.0	4.5	1.0	1.3	3.6	—
8	72 M	IB	—	1.25	43	4.4	3.5	1.4	1.4	3.5	—
9	59 M	IB	3	2.5	27	6.5	5.6	1.3	1.3	3.4	195/50
10	76 M	IB	0	2.06	31	5.6	5.2	1.1	1.0	4.0	—
11	70 F	IB	0	2.63	24	6.3	5.4	1.2	1.2	3.8	—
12	78 M	IB	3	1.38	30	4.4	3.9	1.3	1.3	3.5	185/23
13	88 M	II	0	2.29	26	5.0	4.4	1.4	1.3	3.3	—
14	69 M	II	3	2.63	35	6.1	5.4	1.2	1.0	4.5	140/17
15	54 M	II	0	2.6	24	7.6	7.0	1.1	1.1	4.3	165/35
16	76 M	II	LM	1.75	29	5.9	5.6	1.4	1.3	3.9	185/13
17	82 M	II	—	2.25	36	5.6	4.8	1.2	1.1	4.2	—
18	77 M	II	1	2.0	38	5.2	4.5	1.2	1.2	3.8	204/23

  

Patient	Ao BP (mm Hg)	Pk. Vel. (m/s)		PPG (mm Hg)		MPG (mm Hg)		AVA (cm <sup>2</sup> )		Valve Resist. (dynes•s•cm <sup>-5</sup> )		AVR	1-Year (f/u)
		Bs	Dob.	Bs	Dob.	Bs	Dob.	Bs	Dob.	Bs	Dob.		
1	92/68	3.0	3.6	36	52	17	29	0.7	0.7	152	236	+	A & W
2	112/60	3.8	4.5	58	81	27	45	0.7	0.8	196	211	0	Dead
3	—	3.2	3.9	41	61	24	39	0.8	0.7	196	330	0	Alive
4	109/69	3.6	4.5	52	81	27	44	0.6	0.6	246	323	+	A & W
5	90/62	3.4	4.3	46	74	25	43	0.7	0.8	169	211	+	Dead
6	92/60	3.7	4.9	55	96	30	60	0.6	0.7	254	346	+	A & W
7	—	2.3	3.4	21	46	12	26	0.8	0.9	116	168	0	—
8	—	2.8	3.4	31	46	19	27	0.9	1.2	119	114	0	A & W
9	176/90	2.9	3.5	34	49	19	25	0.8	1.1	145	126	0	Dead
10	104/64	2.7	2.7	29	29	19	18	0.8	1.1	145	99	0	A & W
11	108/48	2.5	2.7	25	29	15	20	0.7	1.1	156	118	0	A & W
12	165/85	2.8	3.2	31	41	19	21	0.8	1.1	155	117	0	A & W
13	124/80	2.9	3.3	34	44	19	25	0.9	1.1	158	123	0	CHF
14	120/68	3.6	3.7	52	55	29	34	0.6	0.7	245	261	0	Dead
15	140/98	2.4	2.6	23	27	13	16	0.9	1.0	115	123	0	Dead
16	150/80	3.3	3.3	44	44	26	28	0.8	0.9	182	172	BVP	Dead
17	—	3.1	3.2	38	41	15	17	0.9	0.8	113	118	0	CHF
18	175/69	3.4	3.5	46	49	24	27	0.6	0.7	258	206	0	CHF

\*Number of major coronary arteries narrowed >50% in diameter.  
A & W = alive and well; Ao BP = aortic blood pressure at catheterization (— = not done or valve not crossed); AVA = aortic valve area; AVR = aortic valve replacement (+ done, 0 not done); Bs = baseline; BVP = balloon valvuloplasty; CAD = coronary artery disease; CHF = congestive heart failure; Dob. = dobutamine; f/u = follow-up; LA = left atrial dimension; LM = left main; LV = left ventricular; LVED = LV end-diastolic dimension; LVEF = LV ejection fraction; LVes = LV end-systolic dimension; LVP = LV pressure at catheterization (— = not done or valve not crossed); MPG = mean pressure gradient; Pk. Vel. = peak velocity of aortic stenosis jet; PPG = peak instantaneous pressure gradient; PWT = posterior wall thickness; Resist. = resistance; RWMS = regional wall motion score; SWT = septal wall thickness.

differences in the change in hemodynamic variables from baseline to dobutamine. All data are reported as mean ± 1 SD. A p value ≤0.05 was considered significant.

Group IA consisted of 7 patients (39%) with contractile reserve but no change in aortic valve area. Group IB consisted of 5 patients (28%) with contractile reserve and a significant increase in aortic valve area. Group II consisted of 6 patients (33%) without contractile reserve. There were no group differences in baseline hemodynamic variables or extent of coronary artery disease (Table I).

Ejection fraction increased from 29 ± 6 to 41 ± 10 after dobutamine in group I (p <0.0001), but did not change in group II (31 ± 7 to 32 ± 14). Regional wall motion score decreased from 2.2 ± 0.6 to 1.7 ± 0.5 (p <0.0001) in group I, but did not change significantly in group II (2.3 ± 0.3 to 2.1 ± 0.3). There were significant

group differences in the response of peak aortic velocity to dobutamine (F = 5.7, p = 0.014), mean gradient (F = 5.2, p = 0.019), aortic valve area (F = 9.8, p = 0.0019), and aortic valve resistance (F = 5.3, p = 0.018). Thus, group IA was characterized by dobutamine-induced increases in peak velocity, mean gradient, and valve resistance with no change in aortic valve area. All patients in group IA had an increase of ≥0.6 m/s in peak velocity and ≥10 mm Hg in mean gradient. In contrast, group IB was characterized by a significant increase in calculated aortic valve area without a significant change in peak velocity, mean gradient, or valve resistance. No hemodynamic variable changed significantly in group II.

In group IA, 5 patients presented with congestive heart failure and 2 others had syncope. In group IB, 4 patients had heart failure and 1 had chest pain. All 6 group II patients had heart failure.

Aortic valve replacement was performed in 4 group IA patients, all of whom had severe calcific AS confirmed at surgical inspection. Surgery relieved symptoms and improved LV function in 3 patients; 1 died perioperatively of pump failure. Surgery was not performed in 3 group IA patients because of cancer (n = 1), pulmonary disease (n = 1), or loss to follow-up (n = 1). The 4 group IB patients with congestive heart failure were treated medically and were alive and well at 1 year; the patient with chest pain had 3-vessel disease and refused bypass surgery. He died suddenly at home 4 months later. No group II patient had surgery; 3 died within 4 months and 3 have persistent congestive heart failure. Severe calcific AS was confirmed in 1 group II patient at autopsy.

Heart rate increased from  $82 \pm 14$  to  $99 \pm 13$  beats/min after dobutamine. Systolic blood pressure increased from  $129 \pm 26$  to  $139 \pm 34$  mm Hg. No patient had lightheadedness, dizziness, or angina; however, 1 had frequent asymptomatic ventricular ectopy requiring cessation of dobutamine at  $15 \mu\text{g}/\text{kg}/\text{min}$ .

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This study demonstrates that dobutamine echocardiography is able to identify 3 distinct hemodynamic subsets in patients with severe AS, low transvalvular gradients, and LV dysfunction. Patients with fixed AS demonstrate increased cardiac output and transvalvular gradient with no change in aortic valve area. Patients with relative AS have an increased aortic valve area but no change in gradient. Finally, patients without contractile reserve have indeterminate AS because they are unable to increase their cardiac output with dobutamine.

Several mechanisms can result in the clinical syndrome of severe AS, a low mean gradient, and LV dysfunction. Correctly differentiating these mechanisms may have therapeutic and prognostic implications. First, LV dysfunction may be a consequence of critical AS. In most patients, chronic pressure overload of AS triggers LV hypertrophy, which normalizes wall stress and preserves LV systolic function. However, if the magnitude of hypertrophy is inadequate, wall stress increases and LV systolic dysfunction ensues.<sup>7-10</sup> In such patients, relief of the pressure overload by aortic valve replacement should improve wall stress and lead to partial or full recovery of LV function. In these patients, dobutamine would be expected to elicit contractile reserve and an increase in mean gradient (group IA).

A second hemodynamic mechanism involves the presence of LV dysfunction due to an underlying cardiomyopathy rather than AS.<sup>10</sup> Accordingly, a hypokinetic left ventricle cannot overcome the initial inertial force required to fully open a moderately stenosed aortic valve.<sup>16,17</sup> As a result, the calculated aortic valve area in the baseline state of a low cardiac output would falsely reflect severe AS. Dobutamine may improve cardiac output and increase aortic valve orifice area, with little change in transvalvular gradient (group IB). Such a response to low-dose dobutamine should identify patients unlikely to benefit from aortic valve replacement.

Last, dobutamine does not augment LV function in some patients, making it impossible to determine whether the calculated valve area represents critical AS or an artifact of a low output state. In our study, such

patients had a very poor prognosis. Larger studies are needed to determine if the high surgical mortality in low gradient, low flow AS is largely confined to group II patients.

Bache et al<sup>11</sup> showed that the Gorlin aortic valve area increases during exercise, a finding attributed to increased flow through the valve leaflets actually resulting in a greater orifice area.<sup>25</sup> However, the ability of the Gorlin formula to measure a true change in valve area during increased cardiac output is questionable because the Gorlin constant is flow dependent.<sup>11-14</sup> Thus, a flow-mediated increase in Gorlin aortic valve area could be due to either a change in valve area or a change in the flow-dependent constant. A distinct advantage of the current study is the use of the continuity equation which lacks an empiric constant and is therefore more accurate than the Gorlin equation in predicting valve area in low flow states.<sup>26</sup>

The concept of valve resistance was reexamined by Ford et al<sup>23</sup> as an index of AS that is less flow dependent than the Gorlin valve area. Cannon et al<sup>17</sup> showed that valve resistance at baseline was able to identify patients with low gradients and severe AS who were found not to have significant AS at surgery. In our study, the change in valve resistance with dobutamine was superior to baseline valve resistance in separating fixed from relative AS. In addition, our data show that valve resistance, but not valve area, is flow dependent in patients with fixed AS, whereas valve area, but not resistance, is flow dependent in those with relative AS.

**The safety of dobutamine echocardiography in coronary artery disease is well established.<sup>27</sup> This study shows that dobutamine can be given safely to patients with AS during noninvasive hemodynamic monitoring. The small number of patients in this study preclude assessment of the effect of dobutamine echocardiography on outcome. A large prospective study is indicated. Although the continuity equation does not contain a flow-dependent constant, its limitations include underestimation of LV outflow diameter and failure to properly align the Doppler beam.<sup>18</sup> However, even if errors in velocity measurement occurred, directional changes should be valid since the transducer locations were identical at baseline and dobutamine infusion.**

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## 5-Fluorouracil Cardiotoxicity with Left Ventricular Dysfunction Under Different Dosing Regimens

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**B**ecause of recent recommendations for adjuvant strategies in patients with breast and colorectal cancers,<sup>1</sup> 5-fluorouracil (5-FU) is increasingly used by medical oncologists as well as by other medical specialists treating cancer patients. It is generally regarded as a well-tolerated, easily administered drug, and although it is not well recognized, 5-FU exhibits a distinct form of cardiotoxicity in up to 15% of patients.<sup>2</sup> Although symptoms are mild and transient in most patients, there are rare instances of severe and even lethal events.

During 1992 and 1993, we observed 6 patients with major cardiotoxicity while undergoing 5-FU treatment (Table I). The total number of patients receiving 5-FU was 231: 5-day regimen with 500 to 600 mg/m<sup>2</sup>/day every 3 to 4 weeks in 201; high-dose 24-hour infusion with 1,600 to 3,000 mg/m<sup>2</sup>/day every week in 30. Symptoms occurred during or within 24 hours of treatment. All affected patients were monitored in an intensive care unit and received nitrates, calcium antagonists, heparin, and morphine. Laboratory parameters remained normal. Echocardiography was performed at least every 48 hours. Four patients required sympathomimetic

drugs and 1 required enoximone to maintain blood pressure and a sufficient cardiac output. Three patients underwent repeat 5-FU therapy after complete resolution of all pathologic findings, resulting in symptomatic recurrences in 2 (1 with ventricular fibrillation requiring cardiopulmonary resuscitation).

5-FU produces a painful cardiopathy, which is neither strictly dose-dependant nor irreversible, and which probably develops only in patients with an individual

**TABLE I** Six Patients with Cardiac Side Effects Receiving 5-Fluorouracil Treatment: Characteristics, Symptoms, and Outcome

	Patient Number					
	1	2	3	4	5	6
Age (yrs) & sex	38M	61M	51M	49F	62F	58F
Cardiac disease	WVW	AF	CAD	0	0	non-Q-wave AMI
5-FU (mg/m <sup>2</sup> × d)	500 × 5 q 4 wk	550 × 5 q 3-4 wk	600 × 5 q 3-4 wk	2,500 × 1 q 1 wk	1,900 × 1 q 1 wk	550 × 5 q 3-4 wk
FA (mg × d)	300 × 5	300 × 5	—	500 × 1	500 × 5	300 × 5
Other drugs	Etoposide	—	Epirubicin	—	—	—
Total 5-FU (mg)	32,000	1,500	2,300	7,000	3,000	3,000
Symptoms/signs						
Angina	+	+	+	+	+	+
Hypotension	+	0	0	+	+	0
Dyspnea	+	0	+	0	0	+
Tachycardia	+	0	+	+	+	0
Arrhythmia	0	0	0	0	+	0
Hypokinesia	Global	Apical	Global	Global	Global	0
Coronary stenosis (angiography)	—	0	—	—	0	0
Recovery	+ (d 7)	+ (d 5)	+ (d 5)	+ (d 5)	+ (d 3)	+
Result of repeat treatment	Symptoms	—	—	Tolerated	VF, AF	—

AF = atrial fibrillation; AMI = acute myocardial infarction; CAD = coronary artery disease; FA = folinic acid; 5-FU = 5-fluorouracil; Total 5-FU: cumulative dose of 5-fluorouracil before symptoms; VF = ventricular fibrillation; WVW = Wolff-Parkinson-White syndrome.

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