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Is the Mitral Valve Area Flow-Dependent in Mitral Stenosis?

A Dobutamine Stress Echocardiographic Study

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OBJECTIVES The purpose of this study was to compare the effect of changes in flow rate on the mitral valve area (MVA) derived from two-dimensional echocardiographic planimetry and Doppler pressure half-time (PHT) methods in patients with mitral stenosis (MS).

BACKGROUND Dobutamine stress echocardiography has been proposed as a means of assessing the severity of MS. However, data regarding the effect of an increase in flow rate on MVA are limited. If MVA is indeed flow-dependent, this has important implications for the assessment of the severity of MS, particularly in the setting of reduced cardiac output (CO).

METHODS Dobutamine echocardiography was performed in 57 patients with isolated MS who were in sinus rhythm. The MVA was determined by planimetry and Doppler PHT methods.

RESULTS Cardiac output increased by ≥50% in 27 patients (group I) and by <50% in 30 patients (group II). In group I, the MVA by planimetry increased by only 10.6 ± 2% and the MVA by PHT increased by 21.9 ± 4.8%. These changes were similar to those observed in group II (10.7 ± 3% and 14.8 ± 4%, respectively; p = NS), despite a much smaller increase in CO. A clinically important change (from the severe to mild category) occurred in only one patient when using the PHT method and in none by planimetry.

CONCLUSIONS Changes in flow rate result in small but clinically insignificant changes in echocardiographic MVA measurement. These methods provide an accurate assessment of MS severity in a majority of patients, independent of changes in flow rate. (J Am Coll Cardiol 2002;40: 1809–15) © 2002 by the American College of Cardiology Foundation

The severity of mitral stenosis (MS) is assessed by measuring transmitral pressure gradients and/or the stenotic mitral valve area (MVA) at the orifice (1). The MVA is one of the major indexes used to categorize severity, guide therapy, and monitor the progression of disease (2). Valve area measurement methods in MS were developed in an attempt to provide a flow-independent assessment of mitral valve stenosis. Historically, this value has been derived from the Gorlin formula, and more recently, by echocardiography. Two-dimensional echocardiographic planimetry (3) and Doppler pressure half-time (PHT) methods yield an anatomic valve area (4). These two methods correlate well with each other and are commonly used techniques for assessing MVA. Hemodynamic studies have suggested that MVA is not constant, but varies with changes in flow (5–8). The significance of these flow-related changes in MVA remains unclear. Flow dependence may occur due to true widening of the orifice with increased flow or due to the flow-rate dependence of the formula. It has been suggested that MVA derived by PHT (PHT-MVA) is flow-dependent (5,6). However, no systematic studies are available in a large number of patients with varying degrees of MS severity, and little is known about the effect of a flow increase on true anatomic MVA. Although PHT is known to be dependent on the heart rate (HR), clinical studies examining the effect of increasing flow volume on Doppler PHT-MVA have not studied the independent effects of an increase in volume versus an increase in HR.

Thus, the data presently available do not clearly prove whether the degree of MS varies with changes in the valve-opening force. Because the determinants of this force are transvalvular flow, transmitral gradient, and flow velocity, the assessment of MS by Doppler or planimetry methods might be altered in low-output states. The purposes of this investigation were to: 1) determine whether anatomic MVA measured by planimetry and MVA derived by PHT change with flow rate; 2) examine the differential effects of an increase in flow on MVA determined by the two methods; and 3) determine whether the flow-related changes in MVA are clinically significant, so as to alter the classification of severity used in clinical decision-making.

METHODS

Study patients. The study protocol was approved by the institutional Research and Ethics Committee. Written, informed consent was obtained from each patient or his or

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Abbreviations and Acronyms

CO	= cardiac output
HR	= heart rate
LVOT	= left ventricular outflow tract
MS	= mitral stenosis
MVA	= mitral valve area
PHT	= pressure half-time
PHT-MVA	= mitral valve area measured by pressure half-time
2DE-MVA	= mitral valve area measured by two-dimensional echocardiography

her guardian. The study included 59 consecutive patients with isolated rheumatic MS who were in sinus rhythm. Two patients were subsequently excluded because of the development of significant ventricular arrhythmia during the dobutamine infusion. The remaining 57 patients who completed the study protocol included 17 males and 40 females (age range 14 to 55 years; mean 29 years). Patients with atrial fibrillation, New York Heart Association functional class IV symptoms, moderate or severe mitral or aortic regurgitation, poor acoustic windows, sinus tachycardia, previous balloon or operative mitral commissurotomy, significant mitral valve calcification, or any systemic illness were excluded.

Transthoracic echocardiography. A transthoracic annular-array, dual-frequency transducer (3.25/2.5 MHz) interfaced to a commercially available ultrasound unit (CFM 800 VingMed, VingMed Sound A/S, Horten, Norway) was used to obtain echocardiographic images. The electrocardiogram was obtained simultaneously, and the HR was calculated from the RR intervals. The entire examination was recorded on 0.5-in. VHS videotape. Patients were examined in the left lateral decubitus position after resting for 30 min and then during dobutamine infusion. For the assessment of intraobserver variability, baseline imaging was repeated after 24 h in 10 patients. The patients underwent a complete echocardiographic examination, including transthoracic imaging, pulsed-wave Doppler, continuous-wave Doppler, and color flow mapping. Two-dimensional echocardiographic measurements included the left ventricular outflow tract (LVOT) diameter, planimetry of the mitral valve orifice in the parasternal short-axis view, and mitral valve score. Pulsed-wave Doppler interrogation of the LVOT was performed to obtain the LVOT velocity-time integral (stroke distance), and continuous-wave Doppler examination of the mitral valve orifice in the apical four-chamber view were recorded to obtain: 1) the diastolic filling period; 2) the peak and mean transmitral pressure gradients; and 3) the transmitral velocity-time integral. The MVA measured by two-dimensional echocardiography (2DE-MVA) was determined off-line at baseline and at steady-state dobutamine infusion. All measurements were obtained by planimetry of the mitral valve orifice area in the parasternal short-axis view at the valve tips by an experienced observer (3). Measurements of MVA were consistently made at the same location, using optimal gain settings. The PHT-MVA was determined using the continuous-wave Doppler spectrum of transmitral flow (4). Cardiac output (CO) was calculated as: (LVOT velocity-time integral) $\times$ 0.785 $\times$ (LVOT diameter)^2 $\times$ (HR) (9). At least five consecutive measurements of MVA were averaged for a given hemodynamic profile. The mitral valve morphologic score was assessed in all patients (10). Based on planimetry, severe MS was defined as MVA $\leq$1 cm^2; moderate MS as MVA 1.1 to 1.4 cm^2; and mild MS as MVA $\geq$1.5 cm^2.

Hemodynamic manipulation. Changes in CO were induced by an infusion of dobutamine. After obtaining baseline echocardiographic and Doppler hemodynamic data, a graded infusion of dobutamine was begun at 5 μg/kg body weight/min and doubled every 5 min until an increase in CO of $\geq$50% or an infusion rate of 20 μg/kg/min was obtained. Repeat echocardiographic and Doppler hemodynamic data were recorded during steady-state dobutamine infusion. Heart rate and sphygmomanometric blood pressure were recorded every 2 min.

Analysis of data. The MVA values obtained by two-dimensional echocardiography and PHT methods were compared at baseline and at a peak dose of dobutamine infusion, with regard to absolute values, percent differences, and categories of MS severity. The absolute difference in MVA, percent change in HR, and percent change in CO were calculated for all patients. Patients were classified into two groups based on the degree of increase in CO after dobutamine infusion: patients in group I had an increase of $\geq$50% in CO from baseline, and group II patients had a CO increase of $<$50%.

Statistical analysis. Results are presented as the mean value $\pm$ SEM. Within each group, data at baseline and at maximal flow conditions were compared using the paired Student *t* test. The percent change from baseline to peak dobutamine infusion was compared between the two groups by using the unpaired *t* test. Differences were considered significant at $p < 0.05$. Interobserver and intraobserver variabilities are expressed as the mean difference $\pm$ SD. The Karl-Pearson coefficient of correlation was used to determine the relationship between changes in MVA and other hemodynamic variables.

RESULTS

Based on two-dimensional echocardiographic planimetry, 22 patients had severe MS (MVA $\leq$1.0 cm^2) and 35 had mild to moderate MS (MVA $>$1.0 cm^2) at baseline. No patients had regional wall motion abnormalities. The baseline characteristics of the study population are shown in Table 1. The mean peak dobutamine dose was 20 $\pm$ 3 μg/kg per min in group I and 16.5 $\pm$ 2 μg/kg per min in group II. Hemodynamic measurements and MVAs at baseline and during dobutamine infusion are shown in Table 2. In group I, the mean mitral gradient increased

Table 1. Baseline Characteristics

Age (yrs)	29.4 ± 1.1 (range 14–55)
Gender (F/M)	40/17
NYHA class (n)	
Class I	2
Class II	17
Class III	38
Class IV	0
Mitral valve score	6.8 ± 0.2 (range 4–10)

NYHA = New York Heart Association.

from 9 ± 2 mm Hg at baseline to 16 ± 4 mm Hg during dobutamine ($p < 0.0001$); in group II, the mean gradient increased from 10 ± 2 mm Hg to 16 ± 3 mm Hg, respectively ($p < 0.0001$). Changes in CO during dobutamine administration are shown in Figure 1. The mean HR increased from 77 ± 3 beats/min at baseline to 117 ± 4 beats/min during dobutamine in group I ($p < 0.0001$), and increased from 83 ± 3 beats/min (at baseline) to 109 ± 4 beats/min during dobutamine in group II ($p < 0.0001$). Twenty-four patients had a mitral valve score >6 (mean 8.13 ± 0.25); these patients demonstrated a small change in 2DE-MVA (1.17 ± 0.07 cm^2 to 1.31 ± 0.08 cm^2, $p = 0.0002$) and in PHT-MVA (1.14 ± 0.07 cm^2 to 1.43 ± 0.09 cm^2, $p = 0.00002$). These changes were similar in magnitude to those of patients (n = 33) with a mitral valve score ≤6 (mean 5.93 ± 0.07): 2DE-MVA increased from 1.24 ± 0.06 cm^2 to 1.37 ± 0.07 cm^2 ($p = 0.0017$); PHT-MVA increased from 1.24 ± 0.06 cm^2 to 1.43 ± 0.08 cm^2 ($p = 0.0041$). Changes in MVA for patients in groups I and II are demonstrated in Figures 2 and 3, respectively, and in Tables 3 and 4. Differences in changes in MVA and hemodynamic variables are shown in Table 5. Changes in 2DE-MVA (10.7 ± 2% vs. 10.7 ± 3%, $p = 0.994$) and PHT-MVA (21.9 ± 4.8% vs. 14.8 ± 4%, $p = 0.25$) were similar in the two groups, despite a significantly greater increase in HR ($p = 0.002$) and CO ($p < 0.00001$) in group I.

A major change in the classification of MS (from the severe to mild category) occurred in only one patient assessed by PHT-MVA and in no patient assessed by 2DE-MVA. Classification changed from moderate to mild in four patients by PHT-MVA and in one patient by 2DE-MVA. Changes in 2DE-MVA did not correlate with changes in CO ($r = -0.04$) or changes in HR ($r = 0.008$).

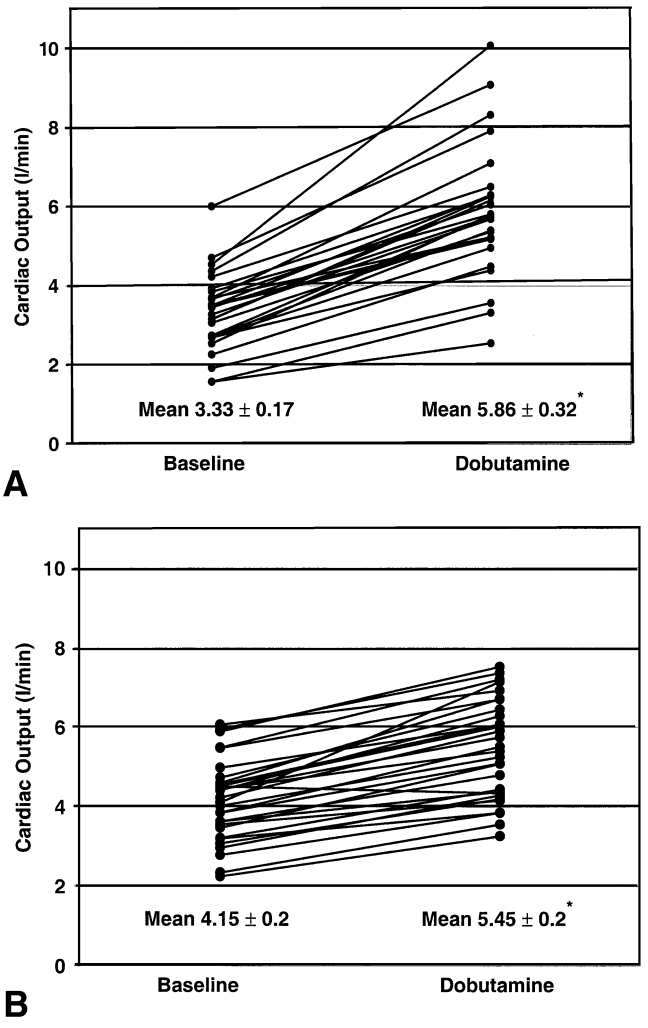

Figure 1. Changes in cardiac output during dobutamine administration in group I **(A)** and group II **(B)**. *$p < 0.0001$ compared to baseline.

Changes in PHT-MVA only correlated weakly with changes in CO ($r = 0.247$, $p = 0.05$), but had a stronger correlation with changes in HR ($r = 0.47$, $p < 0.001$). There was a weak inverse correlation between 2DE-MVA and PHT-MVA changes and baseline MVA ($r = -0.30$ and $r = -0.29$, respectively; $p < 0.05$). The mitral valve score showed no correlation with changes in 2DE-MVA ($r = 0.07$) or changes in PHT-MVA ($r = 0.13$). Intraob-

Table 2. Hemodynamic Measurements and MVA at Baseline and With Dobutamine Infusion

	Baseline	Dobutamine	Mean Change	p Value
HR (beats/min)	80 ± 2	112 ± 3	43.4 ± 4%	< 0.00001
CO (l/min)	3.8 ± 0.2	5.5 ± 0.2	54.7 ± 4%	< 0.00001
Stroke distance (cm)	17.5 ± 4.4	18.7 ± 4.2	—	NS
Mitral inflow TVI	60.2 ± 3.0	62.8 ± 3.1	—	NS
Diastolic filling time (ms)	439 ± 23	327 ± 13	25.4 ± 5%	0.00008
2DE-MVA (cm^2)	1.21 ± 0.05	1.35 ± 0.05	10.7 ± 2%	< 0.00001
PHT-MVA (cm^2)	1.20 ± 0.05	1.43 ± 0.06	19.4 ± 3%	< 0.00001

Data are presented as the mean value ± SEM.
2DE = two-dimensional echocardiographic; CO = cardiac output; HR = heart rate; MVA = mitral valve area; PHT = pressure half-time; TVI = time–velocity integral.

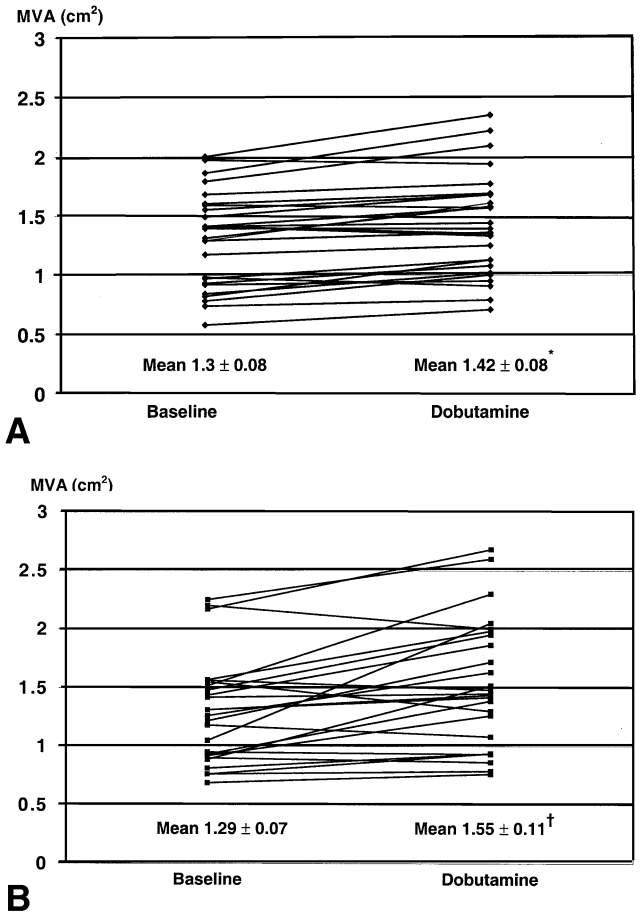

Figure 2. (A) Changes in planimetered mitral valve area (MVA) during dobutamine infusion in group I. **(B)** Changes in MVA derived by the pressure half-time method during dobutamine infusion in group I. *$p <$ 0.0001, †$p = 0.0002$ compared with baseline.

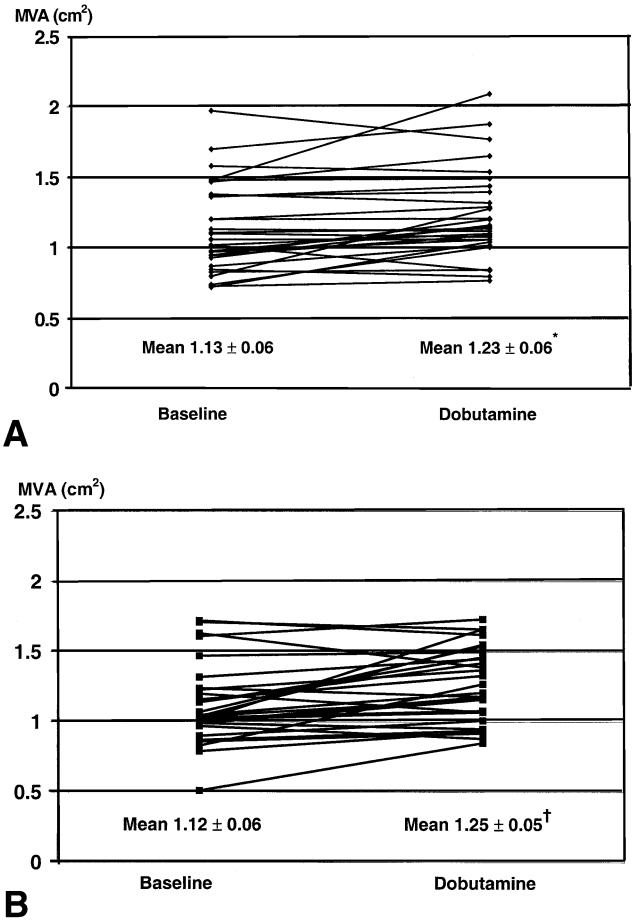

Figure 3. (A) Changes in planimetered mitral valve area (MVA) during dobutamine infusion in group II. **(B)** Changes in MVA derived by the pressure half-time method during dobutamine infusion in group II. *$p =$ 0.0035, †$p = 0.001$ compared with baseline.

server variabilities for 2DE-MVA and PHT-MVA were 3 ± 2% and 5 ± 3%, respectively, whereas interobserver variabilities were 7 ± 3% and 5 ± 3%, respectively.

DISCUSSION

This study demonstrates that alterations in transmitral flow are associated with small but clinically insignificant changes in directly planimetered MVA, as well as somewhat more pronounced changes in MVA determined by PHT. Classification of the severity of MS, as defined by MVA, was not altered in a clinically significant manner in most patients. The MVA reserve in this patient population with rheumatic MS without significant calcification was weakly related to the baseline severity of MS, but not to the flow increase or mitral valve score. However, changes in PHT-MVA had a modest correlation with changes in HR. Slightly more than 50% of the patient population had an increase in CO after dobutamine infusion that was caused predominantly by an increase in HR; even these patients showed a small increase in MVA by both methods that was similar to that of patients whose CO was augmented by an increase in both HR and stroke volume. This observation suggests that an increase in stroke volume is not due to an increase in anatomic MVA in patients with MS.

Earlier invasive hemodynamic studies using the Gorlin formula to calculate MVA have suggested that MVA in patients with MS is independent of flow (11,12), and similar data have been published using the continuity equation (5,7). However, several studies (5,6,8–10,13) have suggested that MVA in MS is flow-dependent, and that this mitral valve "reserve" is dependent on the severity of pathologic changes, as assessed by the mitral valve score (8). Thus, whether MVA is flow-dependent or not is still controversial.

Previous studies of MVA under varying hemodynamic conditions have been limited by the flow dependence and HR dependence of the formulae used to estimate MVA. The MVA determined by the PHT method is rate-dependent, as shown in this study and previous studies (5,14). Potential pitfalls associated with the use of the continuity equation include the difficulty of accurately measuring the LVOT diameter and carefully defining the

Table 3. MVA at Baseline and During Dobutamine Infusion in Group I Patients

Patient No.	Age (yrs)	2DE-MVA (cm^2)		PHT-MVA (cm^2)		CO (l/min)		HR (beats/min)	
		Before	During	Before	During	Before	During	Before	During
1	14	0.74	0.79	0.95	0.93	3.06	5.37	118	132
2	35	1.29	1.36	1.31	1.42	3.85	5.81	83	109
3	37	1.60	1.69	1.31	1.44	3.7	5.23	96	116
4	55	1.41	1.57	1.57	1.98	4.23	6.5	82	99
5	29	0.78	1.0	0.69	0.76	3.7	7.1	49	82
6	42	1.29	1.61	1.26	1.63	4.37	8.32	85	129
7	22	0.97	1.13	1.22	1.72	2.71	5.4	89	115
8	37	1.41	1.44	1.42	1.45	4.54	10.07	102	164
9	28	1.97	1.94	2.17	2.68	2.7	4.96	77	100
10	30	2.0	2.35	2.2	2.0	3.27	5.69	91	112
11	27	1.59	1.57	1.56	1.48	3.16	6.16	61	102
12	33	1.86	2.22	2.25	2.6	3.52	5.22	86	126
13	24	1.17	1.25	0.76	0.94	2.74	5.76	50	91
14	30	1.39	1.39	1.18	1.08	3.45	5.74	82	116
15	20	0.84	1.02	0.9	0.86	4.71	7.91	51	67
16	28	1.49	1.68	1.48	1.95	3.5	6.29	76	152
17	23	1.41	1.33	0.81	0.94	2.54	5.8	56	88
18	45	1.55	1.68	1.44	1.86	3.49	5.18	81	130
19	22	1.79	2.09	1.52	2.3	2.69	4.39	71	111
20	25	0.93	1.08	1.05	2.05	1.92	3.57	81	119
21	30	1.68	1.77	1.57	1.98	3.66	6.05	77	146
22	40	0.58	0.71	0.89	1.52	1.57	3.32	51	126
23	27	1.31	1.58	0.92	1.26	6.01	9.08	61	99
24	25	0.92	0.95	0.76	0.79	1.57	2.55	94	117
25	16	1.41	1.35	1.14	N/A	3.93	6.26	70	146
26	30	0.82	1.13	0.93	1.39	3.15	6.26	69	133
27	17	0.98	0.91	1.55	1.3	2.26	4.49	89	139
Mean ± SEM	29.3 ± 1.8	1.3 ± 0.075	1.42 ± 0.08	1.29 ± 0.07	1.55 ± 0.11	3.33 ± 0.17	5.863 ± 0.32	77 ± 3	117 ± 4
p value			< 0.0001		0.0002		< 0.0001		< 0.0001

Abbreviations as in Table 2.

LVOT velocity before flow acceleration. The Gorlin formula uses a discharge constant that may be influenced by hemodynamic conditions and can decrease in low flow states. Anatomic MVA measured by direct planimetry of the mitral valve orifice has an excellent correlation with PHT-MVA, the Gorlin formula, and the continuity equation at rest (4,5,7). In addition, it has been observed that 2DE-MVA has a strong correlation with direct measurement of the valve orifice at the time of surgery (15). Evaluation of anatomic MVA under varying hemodynamic conditions, therefore, is essential to understand the significance of flow-related changes in MVA obtained by Doppler methods. A true widening of the orifice area could occur with an increase in the opening force, which is related to left atrial pressure, stroke volume, and transmitral flow rate. Alternatively, the increase in MVA with augmented flow could be due to the rate dependence of the formula itself. Our results demonstrate that there is a small degree of true widening of the mitral valve orifice in patients with MS, which is more pronounced in patients with severe MS at baseline and which does not correlate with an increase in flow. This suggests that in untreated MS of varying severity, the mitral valve reserve capacity is finite and reaches its limit with a small increase in flow, beyond which MVA remains relatively constant. The flow dependence of MVA measurement is particularly relevant to the scenario of low CO. These data indicate that the accuracy of planimetry or PHT methods is not compromised in low output states.

Study limitations. The change in flow obtained in our patients with MS was statistically significant but limited. Similar changes in flow with exercise or dobutamine infusion have been reported previously (5–8,11–14,16–18). Because our patients were relatively young and had rheumatic MS without significant valvular calcification, the results may not be applicable to older patients. In addition, it is unknown whether patients with significant subvalvular stenosis would respond similarly. We deliberately excluded patients who had atrial fibrillation, so as to obtain uniformity in data collection. Patients with atrial fibrillation may have low CO, low transmitral gradients, and associated left ventricular dysfunction, and it is unknown whether these data are applicable to such patients (19).

Clinical implications. Measurement of anatomic MVA by planimetry provides strong evidence for the presence of a mitral valve reserve capacity. This reserve capacity is modest and does not alter the classification of severity of MS in a clinically meaningful way. Measurement of MVA by

Table 4. Mitral Valve Area Before and During Dobutamine Infusion in Group II Patients

Patient No.	Age (years)	2DE-MVA (cm^2)		PHT-MVA (cm^2)		CO (l/min)		HR (beats/min)	
		Before	During	Before	During	Before	During	Before	During
1	20	0.87	1.02	0.83	1.27	3.47	5.08	88	139
2	22	1.48	1.49	1.24	1.18	3.85	5.51	74	94
3	28	0.95	1.2	0.87	0.94	4.42	6.29	71	77
4	24	1.2	1.29	0.9	1.01	4.11	7.15	87	107
5	25	1.1	1.08	1.05	1.21	2.34	3.56	99	117
6	40	0.98	1.06	1.04	1.16	4.6	6.72	67	106
7	40	1.06	1.06	1.03	1.07	4.74	6.44	81	119
8	39	1.38	1.32	1.14	1.42	6.07	6.93	111	117
9	22	0.83	0.85	0.86	0.92	3.22	4.44	88	137
10	26	1.02	0.84	1.2	1.07	3.63	4.38	107	130
11	36	0.8	1.28	1.03	1.08	5.96	7.36	91	99
12	33	1.97	1.77	1.71	1.66	4.57	6.08	97	132
13	26	0.97	1.06	0.99	0.95	4.24	5.9	72	101
14	28	1.47	1.65	1.63	1.39	3.2	3.86	74	78
15	35	0.73	0.77	0.97	0.88	3.08	4.2	113	115
16	16	0.74	1.01	0.79	0.93	3.63	4.8	59	76
17	30	1.11	1.14	1.07	1.54	2.25	3.27	59	118
18	24	0.95	1.09	1.02	1.07	2.79	3.85	96	129
19	27	1.37	1.4	1.47	1.5	5.49	7.21	88	126
20	30	0.85	0.8	0.51	0.85	4.98	6.05	64	79
21	36	1.36	1.44	1.04	1.55	3.86	5.09	77	84
22	40	1.2	1.21	1.14	1.46	4.46	5.4	53	79
23	30	0.98	1.15	1.16	1.33	5.48	6.7	80	88
24	25	1.02	1.1	1.32	1.45	3.56	4.16	76	131
25	30	0.93	1.16	0.99	1.16	4.53	6.02	77	118
26	35	0.72	1.04	1.01	1.66	4.45	5.75	82	125
27	20	1.58	1.54	1.61	1.73	4.52	4.35	104	122
28	36	1.13	1.12	1.0	1.18	5.89	7.53	96	107
29	38	1.48	2.09	1.72	1.62	2.97	4.3	76	118
30	24	1.7	1.88	1.23	1.37	4.03	5.25	74	92
Mean ± SEM	29.5 ± 1.3	1.131 ± 0.06	1.23 ± 0.06	1.12 ± 0.06	1.25 ± 0.05	4.15 ± 0.2	5.45 ± 0.2	83 ± 3	109 ± 4
p value			0.00356		0.00100		< 0.0001		< 0.0001

Abbreviations as in Table 2.

planimetry appears to be reliable in the presence of varying flow states. Although a small number of patients may demonstrate flow-related changes in PHT-MVA, the availability of concomitant planimetric measurement of MVA can be useful in clarifying the degree of MS. Thus, MVA measurement by these methods appears to be a reliable tool to assess the severity of MS under changing hemodynamic conditions in the majority of patients.

Table 5. Comparison of Dobutamine Effect on Mitral Valve Area in Groups I and II

	Group I (n = 27)	Group II (n = 30)	p Value
Baseline CO (l/min)	3.3 ± 0.17	4.04 ± 0.2	< 0.01
ΔCO (%)	80.3 ± 4.4	31.3 ± 5.3	< 0.000001
ΔHR (%)	53.9 ± 6	31.6 ± 4.2	0.002
ΔStroke distance (%)	24.4 ± 5	0.5 ± 3	0.0005
Δ2DE-MVA (%)	10.7 ± 2	10.7 ± 3	0.994
ΔPHT-MVA (%)	21.9 ± 4.8	14.8 ± 4	0.25
Mitral valve score	6.5 ± 0.1	7.03 ± 0.3	0.5

Data are presented as the mean value ± SEM.
Δ = change; other abbreviations as in Table 2.

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