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Mitral Regurgitation in Hypertrophic Obstructive Cardiomyopathy: Relationship to Obstruction and Relief With Myectomy

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OBJECTIVES This study examined: 1) the impact of myectomy on postoperative mitral regurgitation (MR) and 2) the association between the severity of MR and the left ventricular outflow tract (LVOT) gradient.

BACKGROUND For patients with hypertrophic obstructive cardiomyopathy (HOCM) and MR, controversy exists as to whether myectomy alone is sufficient in eliminating MR. Furthermore, the relationship between the degree of MR and the LVOT peak gradient has not been well defined.

METHODS We performed pre- and postoperative transthoracic as well as intraoperative transesophageal studies in 104 consecutive patients with HOCM undergoing septal myectomy. Left ventricular outflow tract gradient and the nature of MR were assessed.

RESULTS In the 93 patients without independent mitral valve disease, a relationship was observed between MR severity and the LVOT gradient. Left ventricular outflow tract gradient (mean ± standard deviation) for trivial, mild, moderate and severe MR were: 23.2 ± 19.1, 43.8 ± 25.4, 70.1 ± 21.0 and 104 ± 21.0 mm Hg ($p < 0.001$). Early postoperative, MR was absent or trivial in 80%, mild in 19% and moderate in 1%. None of these patients required additional mitral valve surgery. For patients with independent mitral valve disease ($n = 11$), five required mitral valve surgery as well as myectomy. The remainder had significant reductions in the degree of MR with myectomy alone.

CONCLUSIONS For patients with HOCM and MR not due to independent mitral valve disease, myectomy significantly reduced the degree of MR, without requirement for additional mitral valve surgery. In these patients the severity of MR was directly related to the magnitude of the LVOT gradient. (J Am Coll Cardiol 2000;36:2219–25) © 2000 by the American College of Cardiology

Hypertrophic cardiomyopathy is a condition caused by mutations in sarcomeric proteins, which result in abnormal muscle hypertrophy, particularly in the interventricular septum (1). Dynamic left ventricular outflow tract (LVOT) obstruction and the concomitant mitral regurgitation (MR) both caused by systolic anterior motion (SAM) of the mitral leaflets characterize the obstructive form of this condition. Systolic anterior motion is initiated by rapid LV ejection through an outflow tract narrowed by ventricular septal hypertrophy and anterior displacement of the mitral valve apparatus (2,3). This results in production of a Venturi, or drag forces (4,5), which draw both the mitral leaflets and chordae towards the interventricular septum causing leaflet-septal contact and obstruction at this site (Fig. 1) (3,6–9). We have previously demonstrated that MR is related to SAM of the anterior mitral leaflet and failure of the posterior leaflet to move as much forward as the anterior leaflet (9). This results in an interleaflet gap through which the MR is posteriorly directed into the left atrium (Fig. 2A) (9). In most patients with hypertrophic obstructive cardiomyopathy (HOCM), the MR that is dependent on SAM peaks in mid and late systole (8–11).

Significant MR independent of SAM may occur in up to 10% to 20% of patients with HOCM (3,12). Abnormalities causing independent MR include mitral valve prolapse (MVP) (13), chordal rupture (14), traumatic fibrosis of the anterior mitral valve leaflet from repeated septal contact (3,12,15), marked mitral annular calcification (MAC) and anomalous attachment of a papillary muscle to the anterior mitral valve leaflet (3,12,16). Independent MR is usually directed anteriorly (Fig. 2B) or centrally into the left atrium and is usually holosystolic (Fig. 2C) (9). Some investigators have suggested that, in addition to myectomy, mitral valve replacement is also required in many patients to eliminate MR (17).

Previous angiographic (11) indicator dye dilution (12) and echocardiographic (echo) studies (10) have demonstrated that MR is worse with greater degrees of LVOT obstruction. However, a quantitative relationship between MR severity and LVOT gradient has not been established. The purpose of this echo study was to examine the relationship between the nature and severity of MR and subsequent requirement for mitral valve surgery for patients undergoing surgical myectomy.

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Abbreviations and Acronyms

echo = echocardiography
HOCM = hypertrophic obstructive cardiomyopathy
LVOT = left ventricular outflow tract
MAC = mitral annulus calcification
MR = mitral regurgitation
MVP = mitral valve prolapse
SAM = systolic anterior motion
TEE = transesophageal echocardiography

METHODS

The study group consisted of 104 consecutive patients with HOCM undergoing septal myectomy at the Toronto General Hospital. The diagnosis of HOCM was made when there was echo evidence of asymmetric hypertrophy of the interventricular septum (septal/free wall thickness >1.5/1.0) and a dynamic LVOT gradient. The study population included 68 men and 36 women with a mean (± standard deviation) age of 45 ± 11 years (range 23 to 74 years). The total population of 104 patients was then classified into two groups. Group 1 consisted of 93 patients (89% of the total group), with no significant independent mitral valve abnormality detected by preoperative echo. Group 2 patients (n = 11, 11% of the total group) had significant independent mitral valve disease. Patients were followed in the hypertrophic cardiomyopathy clinic and were on negative inotropic medical therapy (beta-adrenergic blocking agents, disopyramide or a combination) in an attempt to reduce the LVOT gradient. The indications for surgery were persistent disabling clinical symptoms despite optimal medical therapy and evidence of a significant LVOT gradient, either at rest or with provocation.

All group 1 patients (n = 93) underwent myectomy without concomitant requirement for mitral valve surgery. Concomitant operative procedures in this group included: coronary artery bypass surgery (n = 12), releasing of a myocardial bridge (n = 2), aortic valve replacement (n = 2), aortic valve repair (n = 1), VSD repair (n = 1), patent ductus arteriosus closure (n = 1), aortic arch replacement (n = 1) and right ventricular outflow tract resection (n = 2).

In the group 2 patients with independent mitral valve disease, 5 of 11 patients, all with at least moderate MVP, underwent mitral valve surgery in addition to myectomy, with mitral valve repair in four. The other six patients underwent myectomy alone. This study was approved by a human subject ethics committee of the Toronto General Hospital.

Echocardiographic methods. All patients underwent comprehensive preoperative transthoracic echo assessment at a mean (± standard deviation) of 3 (± 2) days before operation to assess the degree and extent of hypertrophy, the severity and direction of MR and the LVOT gradient. The peak LVOT gradient was determined by continuous wave Doppler flow signals across the LVOT. The average of five Doppler signals was taken across the LVOT to ensure accuracy in the determination of LVOT gradient. The pressure gradient across the LVOT was calculated using the modified Bernoulli equation, (peak gradient = $4v^2$) (18). Intraoperative transesophageal studies (TEE) were performed using commercially available echo imaging systems (Hewlett-Packard Sonos 1000, 1500 or 2500 Ultrasound Imaging System; Andover, Massachusetts) with a 5 MHz. multiplane, phased array transducer in 95% of cases and a biplane probe in the remaining 5% of cases. Studies were performed after induction of general anesthesia, before sternotomy and after coming off cardiopulmonary bypass. Preoperatively, an assessment was made about the extent and site of myectomy required, the presence of abnormalities of the mitral apparatus and the degree of MR. Immediate postoperative studies evaluated residual outflow tract gradients, MR and surgical complications. All pressure gradients and measurements of MR jet areas were made using the transthoracic images. All patients also underwent predischarge transthoracic echo studies (mean 5 days postop). Studies were recorded on 0.5 inch videotape for subsequent retrieval and independent analysis by two blinded observers (E.Y. and A.O.).

The MR jet area was measured from the maximal MR jet, either in the four-chamber plane or the frontal long-axis plane. Pulmonary venous flows were obtained from the right and left pulmonary veins, and peak systolic and diastolic flow velocities were calculated. The severity of MR was analyzed off-line using color jet area mapping in combination with the pulmonary venous flow characteristics obtained. Mitral regurgitation was classified as follows: trivial—color jet area was <2.0 cm^2, mild—color jet area 2.0 to 3.9 cm^2, moderate—color jet area 4.0 to 8.0 cm^2 with normal pulmonary venous flow and severe—color jet area >8.0 cm^2 with pulmonary venous systolic blunting of 50% or more or flow reversal (19,20). The two observers remeasured MR jet area and LVOT gradient from 11 preoperative studies to assess observer variability.

Statistical methods. Statistical analysis was performed utilizing SPSS for Windows (Version 8.0). Group 1 and 2 patients were analyzed separately. Continuous variables are expressed as mean ± standard deviation. The peak LVOT gradient was compared with MR jet area by linear regression analyses. The LVOT peak gradient across the four MR groups (trivial to severe) were compared by one way analysis of variance and by paired *t* tests (corrected for multiple comparisons; p = 0.05/6 = 0.008). The relationship between MR jet area (dependent variable), time of echo study (pre- versus postmyectomy) and preoperative MR severity was analyzed using two-way repeated-measures analysis of variance. Categorical variables were compared using Fischer exact test. The significance value for analysis of variance and Fisher exact test was set at 0.05 (two-sided). In the 11 studies that were measured twice by the observers, the variability was expressed as the standard deviation of the difference between the original and repeat measurement as

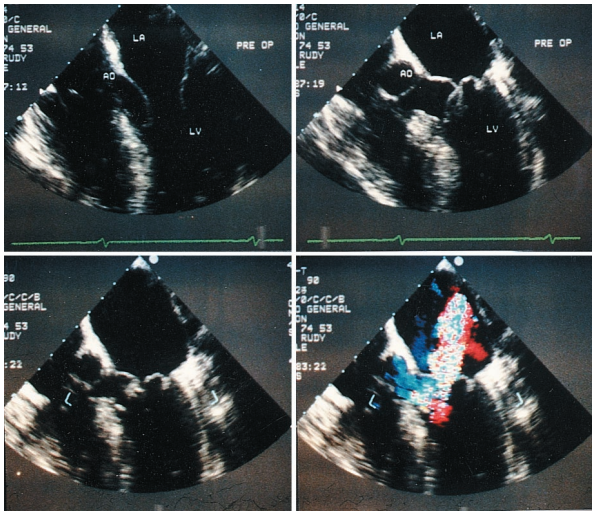

Figure 1. Intraoperative transesophageal echocardiography images demonstrating systolic anterior motion of the anterior mitral valve leaflet **(upper right panel)** and an interleaflet gap **(lower left panel)** through which a jet of mitral regurgitation **(lower right panel)** is centrally directed into the left atrium. The central jet is due to the combination of LVOT obstruction and posterior mitral valve leaflet prolapse. Ao = aorta; LA = left atrium; LV = left ventricle.

well as a percentage of the average of the two measurements (percentage difference).

RESULTS

Preoperative correlation between the degree of MR and the LVOT pressure gradient. Patients without independent mitral valve disease (group 1) were classified as having trivial (n = 25), mild (n = 19), moderate (n = 34) or severe MR (n = 15). There was a corresponding increase in the mean pressure with increasing severity of MR (Table 1). When the peak LVOT gradient of individual patients was plotted against the MR jet area (Fig. 3), the regression line for the group 1 patients was MR jet area = 0.07 gradient + 0.43 (r = 0.85, SEE = 1.65). When patients with a resting gradient of 30 mm Hg or less were excluded, the regression line was MR jet area = 0.07 gradient + 0.92 (r = 0.70, SEE = 1.85). For patients with independent MR (group 2), there was only a weak relationship between the degree of MR and the LVOT gradient, as shown in Table 2. The regression equation for the group 2 patients was y = 0.25 gradient post—0.92 (r = 0.60, SEE = 0.70). The observer variability for the determination of MR jet area and LVOT gradient was 0.2 cm^2 and 2 mm Hg (percentage difference of 5 and 3%, respectively).

Table 1. Relationship Between the Degree of Mitral Regurgitation and LVOT Peak Gradient

MR Classification	MR Jet Area (cm^2)	Mean LVOT Peak Gradient (mm Hg)
Trivial	1.05 ± 0.18*	23.2 ± 19.1*
Mild	2.98 ± 0.42*	43.8 ± 25.4*
Moderate	6.33 ± 0.30*	70.1 ± 21.0*
Severe	9.35 ± 0.96*	104.0 ± 21.0*

Values are expressed as mean ± SD.
*$p < 0.001$ by analysis of variance and pairwise testing.
LVOT = left ventricular outflow tract; MR = mitral regurgitation.

MR jet direction. In group 1 patients MR jet was posteriorly directed in 90/93 (97%) and centrally directed in 3/93 (3%). In these three patients, two were greater than 60 years of age and had mild MAC. This is in contrast with the group 2 patients where a different distribution in jet direction was noted. Although all of these patients had a small posteriorly directed MR jet as a result of SAM, the predominant MR jet direction was either anteriorly or centrally directed. In one patient with bileaflet MVP, the MR was centrally directed. In six patients with posterior leaflet MVP, the jet was anteriorly directed. In the three patients with severe MAC and the patient with mitral stenosis (Fig. 2C), the MR was central. There was a significant difference in the proportion of patients with predominantly posterior directed MR between group 1 and group 2 (97 vs. 0%; [$p < 0.001$]).

Results of myectomy. For each category of preoperative MR in group 1 patients, the pre- and postoperative MR jet

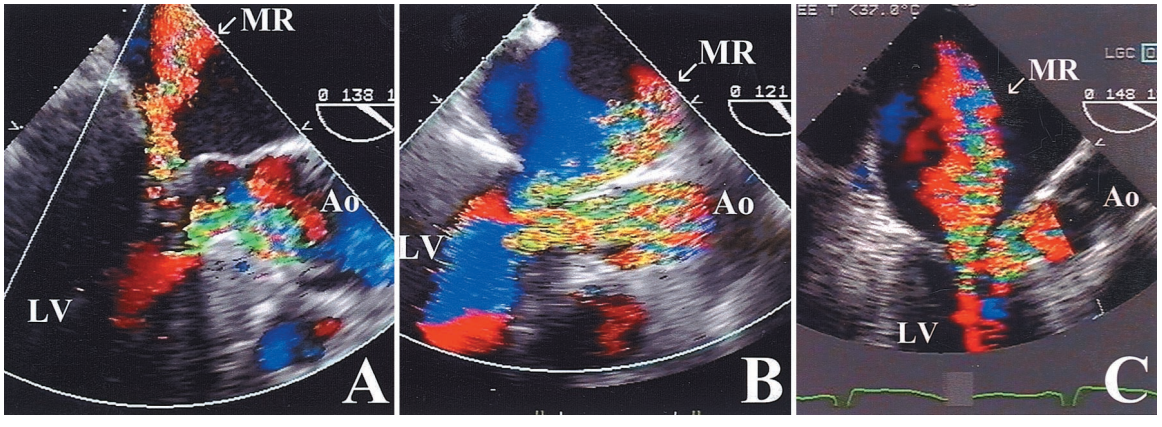

Figure 2. Transesophageal echocardiography images in three patients with hypertrophic obstructive cardiomyopathy showing: **(A)** Posteriorly directed mitral regurgitation jet **(arrow)** in a patient without independent abnormality of the mitral valve. **(B)** Anteriorly directed mitral regurgitation jet **(arrow)** in a patient with posterior mitral valve leaflet prolapse. **(C)** Centrally directed jet of mitral regurgitation **(arrow)** in a patient with mitral stenosis. Ao = aorta; LV = left ventricle; MR= mitral regurgitation.

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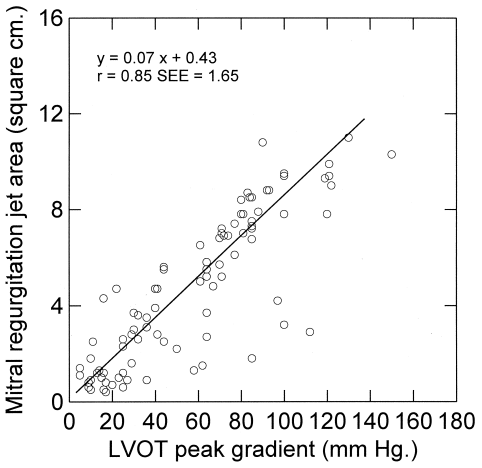

Figure 3. The relationship between the LVOT gradient and the mitral regurgitation jet area. LVOT = left ventricular outflow tract.

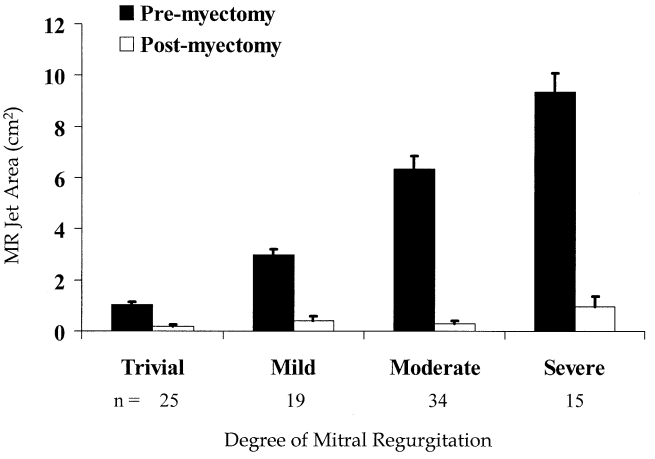

Figure 4. The mitral regurgitation jet area pre- and postmyectomy. MR = mitral regurgitation.

areas were compared (Fig. 4). Postoperatively all patients experienced a significant reduction in the degree of MR. Mitral regurgitation was trivial or absent in 80% (n = 74), mild in 19% (n = 18) and moderate in 1% (n = 1). In this latter patient the residual LVOT gradient was 39 mm Hg (incomplete relief of SAM, LVOT gradient and MR), whereas in all other group 1 patients (92/93) the residual LVOT gradient was <20 mm Hg. Two-way repeated-measures analysis of variance showed a significant effect of time (pre- vs. postmyectomy) and preoperative MR severity on MR jet area ($p < 0.001$ for both comparisons); the interaction between time and preoperative MR severity was also significant ($p < 0.001$).

For group 2 patients with concomitant mitral valve disease, five patients required mitral valve surgery in addition to myectomy. Four patients underwent mitral valve repair for posterior leaflet MVP. In one patient the intraoperative TEE demonstrated the presence of ruptured chords, and severe degrees of MVP was noted in the other three patients. One patient was noted to have severe MR on the immediate postpump TEE. Reexploration revealed inadvertent transection of the mitral chordae, which required mechanical mitral valve replacement. In follow-up these five patients who underwent mitral valve surgery had trace or no MR postoperatively. In the remaining six patients (two MVP, one rheumatic mitral valve, three severe MAC) myectomy alone was performed. In all of these cases there was a significant reduction in the degree of MR from the preoperative state without the requirement for concomitant mitral valve surgery (Table 2). It appears that even in the presence of concomitant mitral valve disease in some cases myectomy alone is sufficient to significantly reduce the degree of MR.

DISCUSSION

Relationship between outflow tract gradient and MR. In patients with HOCM but without intrinsic mitral valve disease, we have demonstrated that myectomy alone is sufficient in eliminating MR. In this same group there is also a quantitative relationship between LVOT gradient and the degree of MR. This relationship is preserved even when patients with resting gradients <30 mm Hg are excluded. We demonstrated that in some patients the degree of dependent MR can be under or overestimated based on the LVOT gradient. While the size of the interleaflet gap causing MR varies directly with the degree of SAM and the

Table 2. Characteristics of Patients With Independent Mitral Regurgitation (Group 2)

Patient	Gender	Age	MV Disease	Concomitant MV Surgery	MRJA Pre-op (cm^2)	LVOT PG Pre-op (mm Hg)	MRJA Post-op (cm^2)
1	M	43	MVP—posterior leaflet	MV repair	7.9	71	1.0
2	M	74	MVP—posterior leaflet	MV repair	9.4	75	1.0
3	F	38	MVP—posterior leaflet	MV repair	6.5	58	1.2
4	F	33	MVP—posterior leaflet	MV replacement	9.2	82	1.0
5	F	40	MVP—posterior leaflet	MV repair	7.8	65	0.0
6	M	33	MVP—posterior leaflet	none	8.5	70	4.1
7	F	50	MVP—bileaflet	none	7.4	60	2.0
8	F	57	Rheumatic mitral stenosis	none	6.9	90	0.8
9	F	59	MAC	none	3.0	36	1.0
10	F	62	MAC	none	6.1	65	1.0
11	M	61	MAC	none	6.8	74	2.2

LVOT = left ventricular outflow tract; MAC = mitral annular calcification; MRJA = mitral regurgitation jet area; MV = mitral valve; MVP = mitral valve prolapse; PG = peak gradient.

obstructive gradient, variations in mitral leaflet length and mobility are also important in determining the degree of MR (21). A previous intraoperative TEE study has shown that both the anterior and posterior mitral leaflets of patients with HOCM are longer than in normal controls (9,21). Residual leaflet tissue after the point of mitral leaflet coaptation is present (9,21). This helps to initiate leaflet SAM but also may reduce the degree of late systolic malcoaptation of the leaflets. An intraoperative TEE study of a group of 23 patients demonstrated that variations in posterior leaflet length and mobility were associated with interindividual differences in the relationship between MR and the LVOT gradient (22). This study suggested that the degree of MR correlated inversely with the length over which the leaflets coapted. Thus, underestimation of the degree of MR can be due to limitations in quantitation by color flow mapping, and jet eccentricity, as well as differences in leaflet angulation.

MR and intrinsic mitral valve disease. Previous discrepancies in the relationship between the severity of MR and the LVOT pressure gradient are also due to the lack of recognition of independent disease of the mitral leaflets, annulus and papillary muscles. While these abnormalities can be recognized by transthoracic studies, they are optimally assessed by TEE. Other mitral valve pathology that has been reported in patients with HOCM include: MVP (13,23), flail posterior leaflet from chordal rupture (14,24), abnormal insertion of a papillary muscle head directly into the anterior mitral leaflet (3,12,16), fibrosis of the anterior mitral leaflet due to repeated leaflet-septal contact (3), leaflet destruction due to endocarditis (25), excessive elongation of the posterior leaflet (26), rheumatic disease as demonstrated in one of our patients and MAC, especially in patients over the age of 50. In all three patients with severe MAC, myectomy alone was adequate to leave only a trace or mild residual MR and avoid difficult mitral annular debridement and valve replacement.

Direction of the MR jet and underlying mitral valve disease. The direction of the MR jet was useful in identifying patients with independent mitral disease and the need for mitral valve surgery. For patients with HOCM, mitral leaflet-septal contact caused a posteriorly directed jet of MR in 97% of our patients in group 1. For patients with associated independent mitral valve disease, significant differences in the direction of the MR jet was noted. When compared with the group 1 patients, none of these patients had isolated posteriorly directed MR jets. This difference in the predominant direction of the MR jet reflects differences in the mechanism responsible for MR between group 1 and group 2 patients.

Intraoperative TEE and surgical decision making. Myotomy or myectomy is an established surgical procedure for symptomatic HOCM unresponsive to medical treatment (27–38). Surgical relief of LVOT obstruction should simultaneously alleviate the MR if SAM is the predominant mechanism for MR. Intraoperative TEE has been shown to be essential in intraoperative decision making for patients undergoing surgical myectomy (9,39). Successful surgery requires adequate resection of subaortic muscle, recognition of the need for concomitant procedures and postoperative confirmation of the adequacy of surgery.

This study demonstrates that successful surgical myectomy can significantly reduce or abolish the degree of MR without the requirement for concomitant mitral valve surgery in all patients without independent mitral valve disease. This usually requires an extensive muscle resection, which can be guided by the TEE. The myectomy should be extended 1 cm below the site of mitral leaflet-septal contact to provide complete relief of the obstruction. The need for revision of the myectomy site was not required in our patients but has been required in up to 14% of patients in other studies (39). Residual MR after successful myectomy should be no worse than mild and can be explained by residual traumatic leaflet thickening or minor degrees of mitral annular calcification.

Concomitant operative strategies at the time for myectomy have attempted to reduce the influence of the increased mitral valve leaflet area and malpositioning of the subvalvular apparatus, thus reducing the risk of persistent SAM and outflow tract obstruction. Although mitral valve replacement was performed as the primary surgical intervention in a significant percentage of patients in several studies (33,37,38,40,41), this strategy exposes patients to the inherent risks of prosthetic valves and anticoagulation therapy. In our institution we have rarely replaced a mitral valve in these patients and have done so only when there is a significant independent abnormality of the mitral valve causing severe MR.

Presently, septal myectomy is still the most frequent operation for this disease (27,42,43). Others have recommended a combination of myectomy with either plication or extension of the mitral leaflet (36,44). Newer surgical approaches including extended and deep ventricular septectomy combined with reconstruction of the subvalvular mitral apparatus have also been suggested (34). However, this study demonstrates that none of these complex procedures are required for successful results.

Study limitations. This study is a retrospective analysis of a selected group of patients at a tertiary referral center. Due to the established surgical expertise of a single surgeon, the operative findings in this study may not be generalizable to other centers due to the variability in surgical technique. Another limitation of this study includes the assessment of MR by the use of MR jet area. Although this is a generally accepted method, the area of the MR jet may have been underestimated due to the eccentricity of these jets as the majority are directed posteriorly (45). However, we feel that, despite the possible underestimation, the results are internally valid, as underestimation of the MR jet would apply to the entire patient cohort and would not bias our results among the four groups of patients. The inaccurate assessment of these eccentric MR jets may also account for some

of the outliers that occur when the MR jet area is plotted against the LVOT pressure gradient.

Conclusions. For patients with HOCM and MR as a result of SAM, myectomy will reduce the severity of MR without the need for additional mitral valve surgery. For patients without independent mitral valve disease, there is a relationship between the LVOT gradient and MR jet area. The presence of posteriorly directed MR can predict with certainty those whose MR will significantly improve with myectomy. For patients with HOCM and concomitant mitral valve disease, mitral valve surgery may be required. However, in some of these patients myectomy alone may be sufficient to abolish or alleviate MR. Echocardiography plays an important role in the prediction of which patients will require a mitral valve procedure in addition to myectomy as well as in perioperative decision making.

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