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ORIGINAL INVESTIGATIONS

First Experience With Percutaneous Mitral Valve Plication as Primary Therapy for Symptomatic Obstructive Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Few therapeutic options exist for patients with severe heart failure due to obstructive hypertrophic cardiomyopathy (HCM) who are at unacceptable surgical risk. We hypothesized that percutaneous plication of the mitral valve could reduce left ventricular outflow tract (LVOT) obstruction and associated mitral regurgitation, thereby leading to amelioration of heart failure symptoms.

OBJECTIVES This study sought to evaluate the potential effectiveness of percutaneous mitral valve plication as a therapy for patients with symptomatic, obstructive HCM.

METHODS Six patients (age 83 ± 8 years; 5 women), judged as not optimal candidates for septal myectomy, were referred for management of severe, drug-refractory heart failure symptoms due to obstructive HCM (New York Heart Association functional class III). Each underwent percutaneous mitral valve leaflet plication to reduce systolic anterior motion (SAM) and mitral regurgitation using the transcatheter mitral clip system.

RESULTS The procedure was completed in 5 patients with placement of a single clip at the A_2-P_2 segments of the mitral valve. One other patient experienced cardiac tamponade, leading to termination of the procedure. Among the 5 treated patients, percutaneous plication with the eliminated SAM and consequently decreased the intraoperative LVOT gradient (91 ± 44 mm Hg to 12 ± 6 mm Hg; $p = 0.007$), left atrial pressure (29 ± 11 mm Hg to 20 ± 8 mm Hg; $p = 0.06$), and mitral regurgitation grade (3.0 ± 0 vs. 0.8 ± 0.4; $p = 0.0002$) associated with improved cardiac output (in $n = 4$; 3.0 ± 0.6 l/min to 4.3 ± 1.2 l/min; $p = 0.03$). Over follow-up of 15 ± 4 months, symptom improvement to New York Heart Association functional class I or II occurred in all patients. Follow-up echocardiography after 15 ± 4 months demonstrated continued absence of SAM and significant reduction in mitral regurgitation, although high systolic LVOT velocities (i.e., >4 m/s) were evident in 3 of the 5 treated patients.

CONCLUSIONS This is a report of percutaneous mitral valve plication as a primary therapy in the management of severely symptomatic, obstructive HCM patients. This initial experience suggests that percutaneous mitral valve plication may be effective for symptom relief in such patients via reduction of SAM and mitral regurgitation. The significance of persistent elevations of LVOT velocities in some patients requires further study. (J Am Coll Cardiol 2016;67:2811–8)

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ABBREVIATIONS AND ACRONYMS

HCM = hypertrophic cardiomyopathy

IQR = interquartile range

LVOT = left ventricular outflow tract

MR = mitral regurgitation

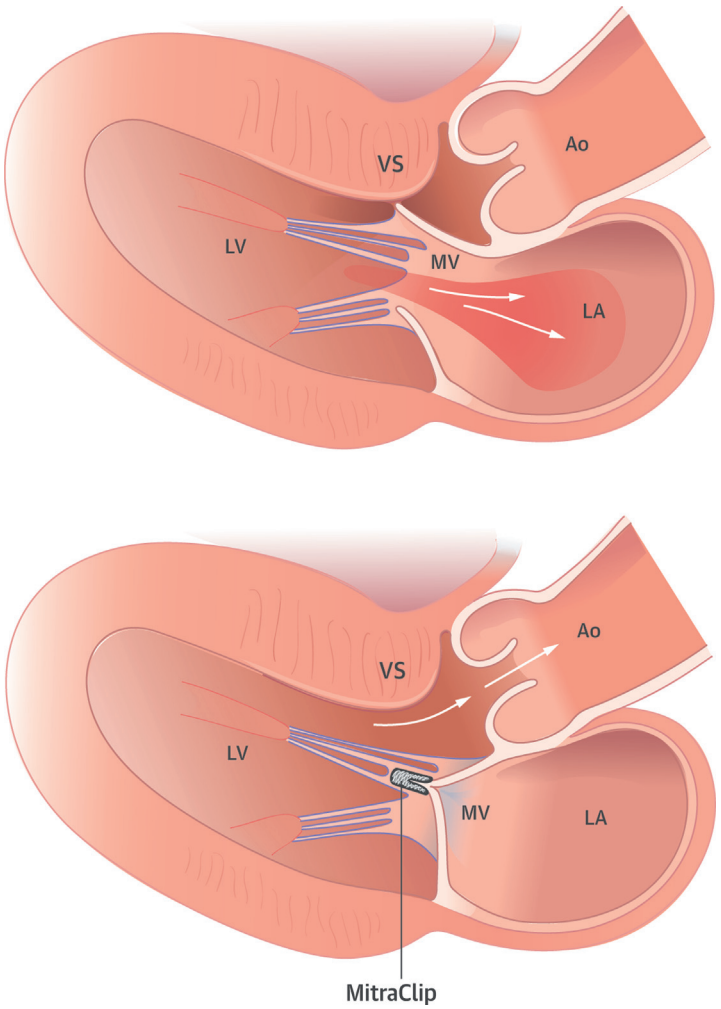
NYHA = New York Heart Association

SAM = systolic anterior motion

Dynamic left ventricular outflow tract (LVOT) obstruction occurs in 70% of patients with hypertrophic cardiomyopathy (HCM) and can be associated with disabling symptoms (1,2). Current therapies for severe, drug-refractory symptoms are surgical septal myectomy (the "gold standard") and alcohol septal ablation (a selective alternative), both of which target the ventricular septum to effectively reduce outflow gradients and relieve heart failure symptoms (3,4). Mitral valve surgery, consisting of either valve replacement or leaflet plication in conjunction with septal myectomy, has been used effectively in obstructive HCM (5,6). Notably, therapeutic targeting of the mitral valve has attracted renewed interest in obstructive HCM with the recent recognition that mitral leaflet elongation and enlargement is common in these patients (7), and transaortic chordal cutting with shallow myectomy has been advanced as a novel surgical strategy (8).

SEE PAGE 2819

CENTRAL ILLUSTRATION Percutaneous Mitral Valve Plication in Hypertrophic Cardiomyopathy



Sorajja, P. et al. J Am Coll Cardiol. 2016;67(24):2811-8.

(Top) Obstructive hypertrophic cardiomyopathy with systolic anterior motion of the mitral valve (SAM) and secondary mitral regurgitation **(arrows)**. **(Bottom)** Following implantation of a MitraClip, both SAM and the secondary mitral regurgitation are reduced. Ao = aorta; LA = left atrium; LV = left ventricle; MV = mitral valve; VS = ventricular septum.

We hypothesized that percutaneous mitral valve plication could be effective in reducing systolic anterior motion (SAM) of the valve and associated mitral regurgitation (MR) in obstructive HCM, thereby providing an alternate strategy for relief of heart failure symptoms. Accordingly, we describe here our experience with percutaneous mitral valve plication using a transcatheter system (MitraClip, Abbott Vascular, Abbott Park, Illinois) in severely symptomatic patients with obstructive HCM. To our knowledge, this report represents the first experience worldwide with percutaneous mitral valve plication employed as an initial interventional therapy for the management of LVOT obstruction in HCM (9).

METHODS

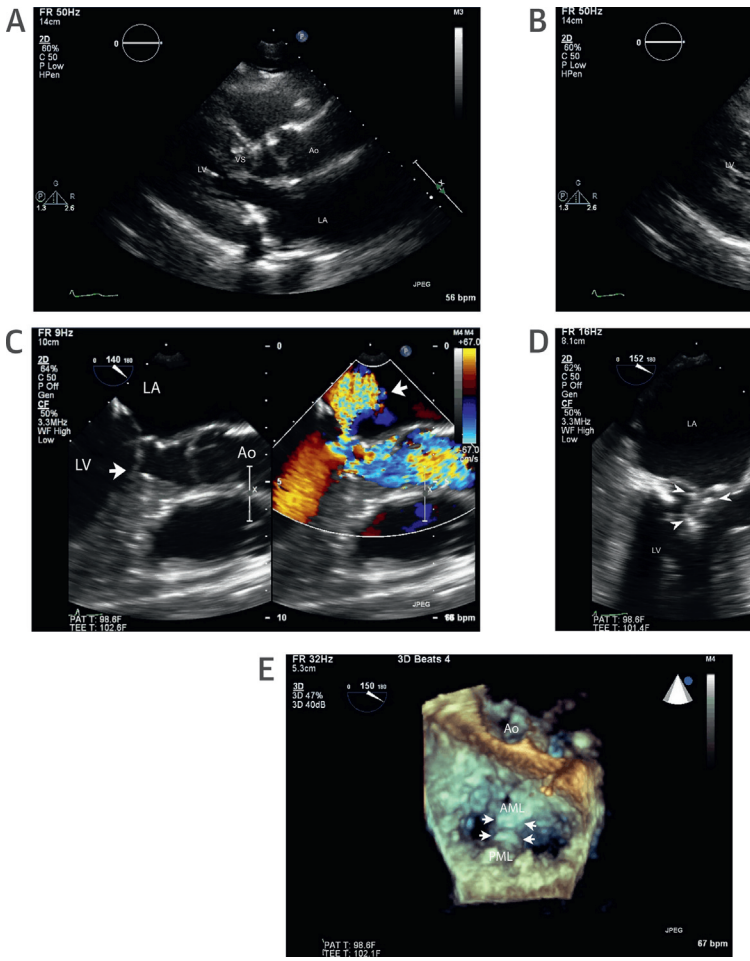
STUDY PATIENTS. Six patients (mean age 83 ± 8 years, range 72 to 90 years; 5 women) with obstructive HCM (ventricular septal thickness 19 ± 3 mm; range 16 to 23 mm) were referred for evaluation and treatment of marked, progressive exertional dyspnea (New York Heart Association [NYHA] functional class III), which had persisted despite escalated doses of negative inotropic agents. In all patients, there was dynamic LVOT obstruction (resting gradients, 61 ± 49 mm Hg) due to elongated mitral valve leaflets and grade III or IV MR. Given their advanced age and general frailty, these patients were initially considered for alcohol septal ablation, rather than surgical myectomy (3). Percutaneous mitral valve plication was offered as an alternative to alcohol ablation. After mitral valve and LVOT anatomy was judged suitable, the patients provided informed consent to proceed with the mitral clip procedure.

PERCUTANEOUS MITRAL VALVE PLICATION. Patients were sedated with general anesthesia, followed by intubation and placement of a transesophageal echocardiography probe for procedural guidance. Baseline and intraprocedural hemodynamic assessments were performed using transseptal catheterization at a puncture site suitable for the procedure and

retrograde aortic cannulation for simultaneous placement of an 8-F Mullins sheath in the left atrium, a 6-F pigtail catheter in the ascending aorta, and a 6-F balloon-tip catheter in the mitral inflow region to avoid catheter entrapment. Cardiac outputs were measured using thermodilution techniques via a standard 7-F pulmonary artery catheter placed through the right internal jugular vein. MR was graded using 2-dimensional and Doppler color-flow imaging with transesophageal echocardiography (10).

Percutaneous mitral valve plication with mitral clip implantation was performed using previously described techniques (11,12). In brief, a posterior-superior transseptal puncture from the right femoral vein was performed at a height of 3.5 to 4.0 cm above the mitral annular plane. Over a stiff wire, a 24-F guiding catheter was placed into the left atrium, followed by advancement of a steerable sleeve and clip delivery system. With guidance from transesophageal echocardiography, the clip delivery system was steered toward the mitral valve with alignment of clip arms perpendicular to the leaflet coaptation plane. The clip was advanced into the left ventricle through a chord-free zone of the mitral valve, followed by

FIGURE 1 Percutaneous Mitral Valve Plication for Obstructive HCM



Pre-procedural parasternal long-axis views at **(A)** end-diastole showing hypertrophy of the anterior basal ventricular septum and **(B)** end-systole demonstrating systolic anterior motion **(arrowhead). (C)** Pre-procedural transesophageal echocardiogram demonstrating systolic anterior motion of the mitral valve **(left, arrow)** and severe mitral regurgitation on color-flow imaging **(right, arrow). (D)** Following implantation of the mitral clip **(left, arrowheads),** systolic anterior motion is now absent and mitral regurgitation is absent on the color-flow image **(right)**. **(E)** Three-dimensional echocardiogram shows creation of the tissue bridge with plication **(arrows)**. AML = anterior mitral leaflet; Ao = ascending aorta; AV = aortic valve; HCM = hypertrophic cardiomyopathy; LA = left atrium; LV = left ventricle; PML = posterior mitral leaflet; RV = right ventricle; VS = ventricular septum (Online Videos 1, 2, and 3).

retraction and grasping of the anterior and posterior leaflets. The clip was decoupled from the delivery catheter following confirmation of adequate leaflet insertion, reduction in the LVOT gradient and MR, and no evidence of severe mitral stenosis on echocardiography. In the event of inadequate or ineffective mitral leaflet grasping, the clip arms were reopened and repositioned.

DATA ANALYSIS. Major adverse clinical events were defined as the occurrence of either stroke, myocardial infarction, major bleeding, or death, using Valve Academic Research Consortium-2 criteria (13). Student *t* tests were utilized for paired comparisons. Data are reported as mean ± SD or median with interquartile range (IQR) where specified.

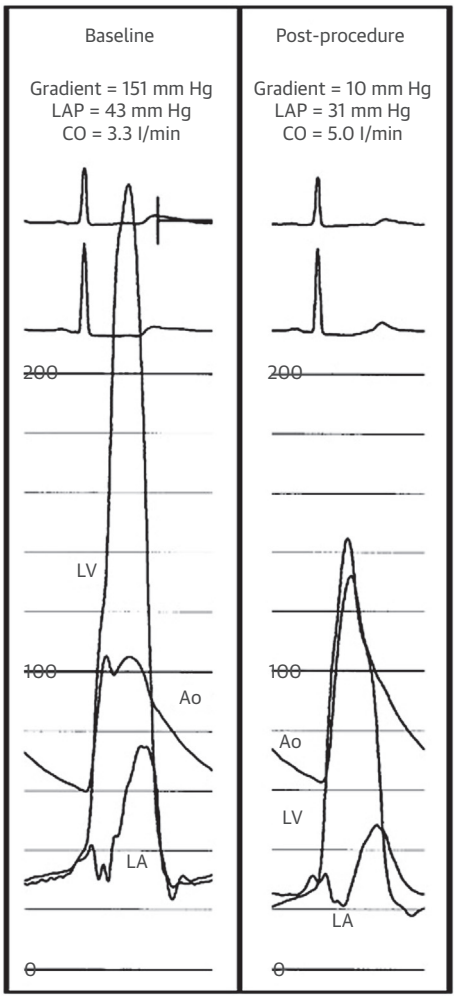
RESULTS

MITRAL CLIP IMPLANTATION. A single clip was successfully implanted in the A_2-P_2 region of the mitral valve in 5 patients (**Central Illustration**). In 1 other patient, cardiac tamponade requiring pericardiocentesis occurred during transseptal puncture, and the procedure was aborted without clip implantation. This patient underwent successful surgical repair and was discharged from the hospital to home health care. Clip implantation was performed with orientation of the clip arms orthogonal to the commissural plane of the mitral valve, as conventionally described for patients with degenerative or functional MR (**Figures 1 and 2**) (11,12). No patient required more than 1 clip. Procedure time, measured from guide insertion to final clip deployment, was a median of 53 (IQR: 44 to 69) min.

PROCEDURE OUTCOME. In the 5 study patients, on echocardiography in the cardiac catheterization laboratory, SAM of the mitral valve was eliminated. Clip implantation led to reduction in the LVOT gradient (91 ± 44 mm Hg to 12 ± 6 mm Hg; p = 0.007), left atrial pressure (29 ± 11 mm Hg to 20 ± 8 mm Hg; p = 0.06), and MR grade (3 ± 0 vs. 0.8 ± 0.4; p = 0.0002). In 4 patients, cardiac output was measured, increasing from 3.0 ± 0.6 l/min to 4.3 ± 1.2 l/min (p = 0.03).

One patient (#1 in **Tables 1 to 3**), pre-procedure had a reduced mitral valve area of 2.8 cm^2; the mitral valve gradient became severe with complete clip closure (mean mitral gradient: 10 mm Hg). The clip was then deployed with partially open arms (i.e., 30°), which proved effective in reducing both the LVOT gradient and MR, while reducing the degree of mitral stenosis (post-implantation mean mitral gradient: 6 mm Hg; heart rate: 59 beats/min). Overall, post-implantation mean mitral gradient in the 5 treated patients was median (IQR) of 3.0 (3.0 to 4.0) mm Hg.

FIGURE 2 Intraprocedural Hemodynamics



(Left) Baseline evaluation demonstrated severe left ventricular outflow tract obstruction of 150 mm Hg with increased left atrial pressure (LAP). **(Right)** Immediately following mitral clip implantation, left ventricular outflow tract gradient decreases to 10 mm Hg, with a fall in mean LAP and rise in cardiac output (CO). Abbreviations as in **Figure 1**.

Each of the 5 study patients was discharged without major adverse clinical events during hospitalization, with a median length-of-stay of 2 (IQR: 2 to 2) days.

FOLLOW-UP DATA. Post-procedural follow-up duration was 15 ± 4 months (range 10 to 19 months). At the most recent evaluation, all 5 patients demonstrated symptom improvement from pre-procedural NYHA functional class III (i.e., decrease by at least 1 functional class), including 3 patients who became asymptomatic (class I; Patients #2, #3, and #5) and 2 with mild residual exertional dyspnea (class II;

Patients #1 and #4); all 5 patients showed persistent reduction in MR grade to 0 or 1 (Online Videos 1, 2, and 3).

One patient (#2) had evidence of pulmonary hypertension (estimated right ventricular systolic pressure: 70 mm Hg) in the setting of systemic hypertension (systolic blood pressure at time of echocardiographic follow-up: 165 mm Hg), as well as a history of pulmonary fibrosis. The 2 patients (#1 and #4) with mild symptoms at follow-up had mean mitral valve gradients ≥4 mm Hg immediately after clip deployment, and 5 mm Hg and 8 mm Hg, respectively, at follow-up, consistent with moderate mitral stenosis. These 2 patients with residual mild symptoms (#1 and #4) and a third asymptomatic patient (#3) showed post-procedural LVOT velocities >5.0 m/s in the absence of SAM on transthoracic echocardiographic studies performed both within a day after the procedure and at the last follow-up evaluation.

HEMODYNAMIC EVALUATION OF INTRACAVITARY GRADIENT. Due to the observation in 3 patients (#1, #3, and #4), who showed high peak LVOT velocities by Doppler echocardiography on follow-up, despite relief of resting outflow gradient, we elected to study 1 of these patients (#5) with simultaneous invasive hemodynamics and echocardiography (**Figure 3**). Following a steady-state period of 10 min, isoproterenol was administered intravenously (5 μg/min) and the LVOT gradient was measured simultaneously with echocardiography and transseptal catheterization (14). We identified a discrepancy between the direct catheter-based measurement of the LVOT gradient (22 mm Hg) and the substantially higher Doppler-estimated gradient (64 mm Hg) (**Figure 3**).

DISCUSSION

The present study of percutaneous mitral valve plication as a primary interventional therapy for patients with symptomatic obstructive HCM demonstrates the feasibility of this therapy, as well as the need for further study to define its ultimate clinical efficacy.

For this subgroup of patients, surgical myectomy is considered the primary option, with alcohol ablation regarded as a therapeutic alternative (3). Both of these strategies target the ventricular septum with septal reduction and have established efficacy when performed in experienced centers (3,4). As an alternative approach, plication of the mitral valve directly addresses the pathophysiology of dynamic LVOT obstruction by specifically targeting the mitral valve and SAM, as well as MR. In patients with HCM, mitral valve leaflet elongation has been shown to be directly related to the presence and magnitude of subaortic obstruction, and independent of age and septal thickness (7).

Percutaneous treatment with the mitral clip system is an established therapy for patients with mitral valve regurgitation (11,12). The underlying principle of mitral clip therapy is percutaneous plication of the mitral valve leaflets with precision, thereby enhancing leaflet coaptation and reducing MR. In patients with HCM, it is notable that LVOT obstruction is not present at onset of systole, but develops during left ventricular ejection in mid-systole due to SAM of the mitral valve and septal contact. By directly plicating the valve leaflets and preventing

TABLE 1 Baseline Characteristics and Pre-Procedural Echocardiographic Data

	All Patients	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Age, yrs	83 ± 8	87	90	75	72	89
Sex	4 F/1 M	F	F	M	F	F
VS, mm	19 ± 3	18	16	17	23	18
LVOT gradient, mm Hg						
Resting	61 ± 49	61	44	20	144	36
Provocable	91 ± 10	NP	81	100	NP	92
MR grade	3.2 ± 0.4	3	3	3	3	4
EDD, mm	40 ± 5	38	41	41	32	46
PASP, mm Hg	37 ± 8	N/A	48	38	33	29
Mitral gradient, mm Hg	1.8 ± 1.1	3	3	1	1	1

Values are mean ± SD unless otherwise indicated.

EDD = end-diastolic dimension; F = female; LVOT = left ventricular outflow tract; M = male; MR = mitral regurgitation; N/A = not available; NP = not performed due to high resting left ventricular outflow tract gradient; PASP = pulmonary artery systolic pressure; VS = ventricular septal thickness.

TABLE 2 Hemodynamic Data Obtained in Cardiac Catheterization Laboratory Before and After Percutaneous Mitral Plication

	All Patients	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
LVOT gradient, mm Hg*						
Baseline resting	91 ± 44	60	45	81	151	120
Post-implantation resting	12 ± 6	17	3	13	10	16
MR grade†						
Baseline	3 ± 0	3	3	3	3	3
Post-implantation	0.8 ± 0.4	1	1	0	1	1
Cardiac output, l/min*						
Baseline	3.0 ± 0.6	3.4	2.2	3.2	3.3	NP
Post-implantation	4.3 ± 1.2	5.2	2.5	4.6	5	NP
Mitral gradient*						
Baseline	1.6 ± 0.9	3	2	1	1	1
Post-implantation	3.6 ± 1.5	6	2	3	4	3
LAP, mm Hg*						
Baseline	29 ± 11	27	23	15	43	37
Post-implantation	20 ± 8	23	22	10	31	17

Values are mean ± SD unless otherwise indicated. *Obtained at cardiac catheterization. †Obtained by echocardiography.

LAP = left atrial pressure; other abbreviations as in Table 1.

TABLE 3 Clinical and Echocardiographic Data at Follow-Up

	All Patients	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5
Follow-up duration, months	15 ± 4	19	16	12	16	10
LVOT velocity, m/s	3.8 ± 2.3	5.2	0.8	5.1	6.2	1.9
MR grade	0.6 ± 0.5	1	0	0	1	1
PASP, mm Hg	42 ± 19	36	70	28	N/A	32
Mitral valve gradient	3 (3-5)	8	3	3	5	3
NYHA functional class	1.4 ± 0.5	2	1	1	2	1

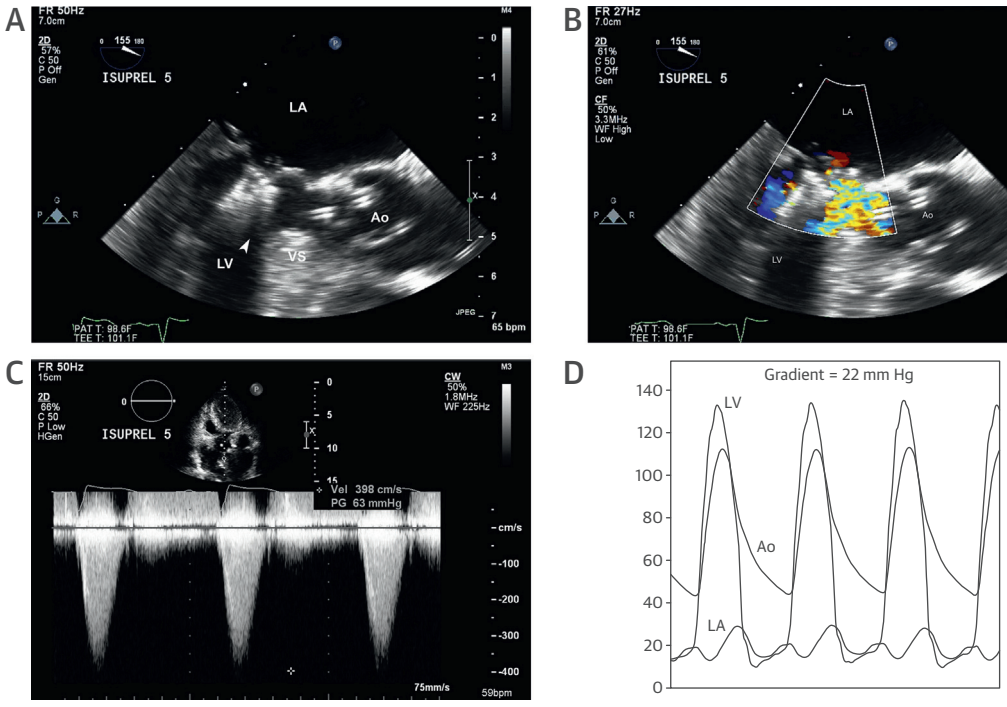
Values are mean ± SD or median (interquartile range), unless otherwise indicated.
NYHA = New York Heart Association; other abbreviations as in Table 1.

SAM, the implanted mitral clip thereby prevents mitral-septal contact, increases LVOT area, normalizes LV pressure, relieves MR, and consequently alleviates heart failure symptoms.

Following mitral clip implantation, there was immediate relief of LVOT obstruction and MR, in association with a fall in left atrial pressure and rise in cardiac output. In clinical follow-up after 15 ± 4 months, all patients reported symptom improvement by at least 1 NYHA functional class, and further intervention was not required. Although use of mitral clip therapy in HCM has been reported previously in a single patient following unsuccessful surgical myectomy, our observations are novel, demonstrating in a series of patients the feasibility of percutaneous mitral valve repair as a primary treatment strategy for selected patients with obstructive HCM (9).

Of note, markedly elevated systolic velocities across the LVOT were evident on follow-up echocardiography in 3 study patients. This occurred despite abolition of SAM by the mitral clip, previous documented relief of obstruction by cardiac catheterization immediately after clip implantation, and improvement in heart failure symptoms. This circumstance of high systolic velocities near the clip in the absence of true impedance to LV outflow has been reported in an HCM patient with a similar clinical scenario (15), reminiscent of the pressure-recovery phenomena observed in patients with aortic stenosis or with small aortic dimension after valve replacement (16-18). To investigate these unexplained outflow

FIGURE 3 Hemodynamic Evaluation of Patient #5 With Simultaneous Cardiac Catheterization and Transthoracic Echocardiography



Immediately following mitral clip placement, this patient had a residual left ventricular outflow tract (LVOT) gradient of 14 mm Hg at rest. Isoproterenol was administered intravenously (5 μg/min). **(A)** LVOT is patent in systole during intravenous administration of isoproterenol with the mitral clip in place **(arrowhead). (B)** Color flow imaging now shows absence of mitral regurgitation. **(C)** Doppler echocardiography shows a peak LVOT velocity of 4.0 m/s and estimated gradient of 64 mm Hg. **(D)** On simultaneous catheterization, the LVOT gradient is only 22 mm Hg. Abbreviations as in Figure 1.

tract velocities after mitral clip implantation, we performed simultaneous echocardiography and invasive hemodynamics in 1 of our study patients, which demonstrated a 3-fold higher Doppler-derived LVOT gradient (64 mm Hg) compared with that observed with cardiac catheterization (22 mm Hg), suggesting that the velocity in the LVOT did not reflect true impedance to LV outflow and did not imply an inadequate hemodynamic result. Potentially, high velocities could arise from placement of the mitral clip in a small LVOT with downstream pressure recovery. Relevant to this hypothesis, all patients selected for the present study were elderly, with the small LV outflow area typical of this advanced age group, in which the mitral valve is in an exaggerated anterior position, and mitral-septal contact is effected by the combination of mitral leaflet anterior motion and posterior ventricular septal excursion, in the absence of the acute anterior leaflet bend more typical of young patients with obstructive HCM (19). Invasive examination of velocities within the left ventricle immediately proximal and distal to the mitral clip (i.e., left ventricular to LVOT gradient) could help address the possibility of pressure recovery.

Due to its established efficacy and safety profile, septal reduction with surgical myectomy remains the primary therapy for most patients with symptomatic obstructive HCM (3). Importantly, among patients who may be considered for the alternative of alcohol septal ablation, 15% to 20% lack appropriate septal artery anatomy or experience incomplete relief of LVOT obstruction with this procedure; also, concern remains regarding the possibility of acute complications and the potential long-term arrhythmic consequences of the alcohol-induced myocardial infarction in some patients (20–22).

STUDY LIMITATIONS. We wish to emphasize that the experience with percutaneous mitral valve plication in obstructive HCM reported here is early and in only a small number of patients, with the appropriate selection of those who are likely to benefit from this treatment currently incompletely resolved. Certainly, there are inherent risks for percutaneous mitral valve plication, which remains technically challenging. Nevertheless, the mitral clip represents a novel alternative treatment option to alcohol septal ablation, which may prove to be an effective therapy for many patients with obstructive HCM. The mitral clip affords several potential advantages: 1) it directly targets the mitral valve and the mechanism of LVOT obstruction; 2) it is less invasive and does not require an iatrogenic septal infarction or ventricular remodeling, avoiding the risk of pacemaker-dependency arrhythmias; 3) hemodynamic efficacy can be assessed prior to permanent clip decoupling, with the capability to fully retrieve the device and permit surgery; and 4) the procedure is not dependent on coronary anatomy nor on the magnitude of ventricular septal hypertrophy.

CONCLUSIONS

If deemed efficacious with further study, percutaneous mitral valve plication could represent a viable option for some patients with severely symptomatic, drug-refractory obstructive HCM, including those who are elderly or with unacceptable risk for surgical myectomy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Percutaneous mitral valve plication with the mitral clip may be effective for symptom relief in patients with obstructive HCM via reduction of SAM and MR.

TRANSLATIONAL OUTLOOK: The present study is the first report of percutaneous mitral valve plication with the mitral clip as a primary therapy for obstructive HCM. Further study on the outcomes of this therapy in a larger population of patients with HCM is needed.

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KEY WORDS cardiac catheterization, hemodynamics, mitral valve insufficiency, mitral valve repair, transcatheter

APPENDIX For supplemental videos and their legends, please see the online version of this article.