Journal of the American College of Cardiology Vol. 57, No. 16, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.043

The Acute Hemodynamic Effects of MitraClip Therapy

Robert J. Siegel, MD,* Simon Biner, MD,* Asim M. Rafique, MD,* Michael Rinaldi, MD,† Scott Lim, MD,‡ Peter Fail, MD,§ James Hermiller, MD,‖ Richard Smalling, MD, PHD,¶ Patrick L. Whitlow, MD,# Howard C. Herrmann, MD,** Elyse Foster, MD,†† Ted Feldman, MD,‡‡ Donald Glower, MD,§§ Saibal Kar, MD,* for the EVEREST Investigators

Los Angeles and San Francisco, California; Charlotte and Durham, North Carolina; Charlottesville, Virginia; Houma, Louisiana; Indianapolis, Indiana; Houston, Texas; Cleveland, Ohio; Philadelphia, Pennsylvania; and Evanston, Illinois

Objectives The objective of this study was to evaluate the acute hemodynamic consequences of mitral valve (MV) repair with the MitraClip device (Abbott Vascular, Menlo Park, California).

Background Whether surgical correction of mitral regurgitation (MR) results in a low cardiac output (CO) state because of an acute increase in afterload remains controversial. The acute hemodynamic consequences of MR reduction with the MitraClip device have not been studied.

Methods We evaluated 107 patients with cardiac catheterization before and immediately following percutaneous MV repair with the MitraClip device. In addition, pre- and post-procedural hemodynamic parameters were studied by transthoracic echocardiography.

Results MitraClip treatment was attempted in 107 patients, and in 96 (90%) patients, a MitraClip was deployed. Successful MitraClip treatment resulted in: 1) an increase in CO from 5.0 ± 2.0 l/min to 5.7 ± 1.9 l/min ($p = 0.003$); 2) an increase in forward stroke volume (FSV) from 57 ± 17 ml to 65 ± 18 ml ($p < 0.001$); and 3) a decrease in systemic vascular resistance from 1,226 ± 481 dyn·s/cm^5 to 1,004 ± 442 dyn·s/cm^5 ($p < 0.001$). In addition, there was left ventricular (LV) unloading manifested by a decrease in LV end-diastolic pressure from 11.4 ± 9.0 mm Hg to 8.8 ± 5.8 mm Hg ($p = 0.016$) and a decrease in LV end-diastolic volume from 172 ± 37 ml to 158 ± 38 ml ($p < 0.001$). None of the patients developed acute post-procedural low CO state.

Conclusions Successful MV repair with the MitraClip system results in an immediate and significant improvement in FSV, CO, and LV loading conditions. There was no evidence of a low CO state following MitraClip treatment for MR. These favorable hemodynamic effects with the MitraClip appear to reduce the risk of developing a low CO state, a complication occasionally observed after surgical MV repair for severe MR. (A Study of the Evalve Cardiovascular Valve Repair System Endovascular Valve Edge-to-Edge Repair Study [EVEREST I]; NCT00209339 and EVEREST II; NCT00209274) (J Am Coll Cardiol 2011;57:1658–65) © 2011 by the American College of Cardiology Foundation

Surgical mitral valve (MV) repair to create a double orifice valve was first performed by Alfieri in 1991 (1–3). A recently introduced MV repair method uses a clip (MitraClip, Abbott Vascular, Menlo Park, California) in a transcatheter closed-chest intracardiac procedure that simulates the Alfieri technique (4). Data on 107 patients of nonrandomized patients enrolled in EVEREST I and in the roll-in phase of EVEREST II demonstrated acute reduction to ≤2+ mitral regurgitation (MR) at discharge in approximately 75% of patients (5,6).

From the *Cedars-Sinai Medical Center, Los Angeles, California; †Sanger Heart and Vascular Institute, Charlotte, North Carolina; ‡University of Virginia, Charlottesville, Virginia; §Terrebonne General Medical Center, Houma, Louisiana; ‖The Care Group, Indianapolis, Indiana; ¶Houston Health Sciences Center, Houston, Texas; #The Cleveland Clinic, Cleveland, Ohio; **University of Pennsylvania, Philadelphia, Pennsylvania; ††University of California at San Francisco, San Francisco, California; ‡‡Evanston Hospital, Evanston, Illinois; and the §§Duke University Medical Center, Durham, North Carolina. Dr. Siegel is a speaker for Philips Ultrasound and a consultant for Abbott. Dr. Rinaldi is on the advisory boards of Abbott, Boston Scientific, and Cordis. Dr. Lim is a consultant to and receives research funding from Abbott Vascular. Dr. Fail is on the medical advisory board for and has stock options in CardioSolutions. Dr. Hermiller is a consultant for Abbott Vascular. Dr. Smalling receives grant support from Evalve. Dr. Whitlow receives research support from Evalve. Dr. Hermann receives research funding from Evalve and Abbott and has equity in and is a consultant to Endovalve. Dr. Foster receives grant support from Evalve, Boston Scientific, EBR Systems, and GDS Systems. Dr. Feldman receives research support and is a consultant to Abbott and Edwards. Dr. Kar receives research grants and honoraria from and is a consultant to Abbott Vascular. All other authors have reported that they have no relationships to disclose. Drs. Siegel and Biner contributed equally to this work.

Manuscript received October 13, 2010; revised manuscript received October 22, 2010, accepted November 3, 2010.

One of the concerns with surgical correction of MR has been the potential increase in left ventricular (LV) afterload owing to elimination of the low-impedance regurgitant flow into the left atrium (LA). An increase in afterload associated with correction of MR could impair LV systolic performance (7–9) and may result in an acute post-operative low cardiac output (CO) state (9–13). The significance of this phenomenon in patients with surgically corrected MR by valve replacement or repair is controversial because the consequences of MR elimination are confounded by numerous factors owing to the nature of open heart surgery and the effects of cardiopulmonary bypass and cardioplegic arrest.

Because the MitraClip procedure does not require cardiopulmonary bypass, it provides a unique opportunity to assess the acute hemodynamic changes solely attributable to reduction of MR. The objective of this analysis was to characterize the impact of reduction in MR with the MitraClip therapy on intraprocedural CO and hemodynamics.

Methods

We studied 107 patients, 55 treated in the EVEREST (A Study of the Evalve Cardiovascular Valve Repair System Endovascular Valve Edge-to-Edge Repair Study) phase I feasibility trial (14), and 52 roll-in patients treated in the EVEREST II pivotal trial, who represent the pre-randomization experience.

Patient characteristics, echocardiographic protocol, and procedural technique have recently been described (6,14,15). Symptomatic patients with moderate to severe (3+) or severe (4+) MR or asymptomatic patients with the same MR severity and abnormal LV systolic function (left ventricular ejection fraction [LVEF] <60% or LV end-systolic dimension >40 mm) underwent MitraClip treatment in accordance with the ACC/AHA guideline indications for MR surgery (16). As shown in Table 1, MR was graded according to the criteria of the American Society of Echocardiography (17). Three of the 6 criteria listed in Table 1, at least one of which was quantitative, had to be present for classification of MR as severe or moderate to severe.

The procedure was performed under general anesthesia using transesophageal echocardiography guidance and fluoroscopy. Vascular access was established from the femoral vein. The MitraClip device was advanced following an echocardiography-guided transseptal approach to the LA and across the MV to the LV. The arms of the clip were oriented perpendicular to the line of leaflet coaptation, the leaflets were grasped, and the clip was closed while reduction of MR severity was assessed by Doppler echocardiography. A second MitraClip device was placed if further reduction of MR was needed. Transthoracic echocardiographic (TTE) images were obtained using a detailed echocardiographic protocol after face to face training of sonographers in participating centers. All quantitative measurements including regurgitant volume, regurgitant fraction (RF), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and forward stroke volume (FSV) as well as MR and TR grades from +1 to +4 were made at the core laboratory (University of California at San Francisco) (15).

Cardiac catheterization. All hemodynamic measurements were taken while the patients were under general anesthesia. Patients were studied according to the protocol before and within 15 min following attempted clip deployment regardless of procedural success.

Transducers were balanced by determining zero level at the mid-axillary line. LV peak end-systolic and peak end-diastolic pressures (LVEDP) were reported. Arterial pressures were measured from the femoral artery. Left atrial pressure was obtained from the transseptal catheter positioned in the LA or by measurement of pulmonary capillary wedge pressure (PCWP) using a balloon-tipped Swan-Ganz catheter. Wedge position was verified by fluoroscopy and phasic changes in pressure waveforms. The values of PCWP were assessed at end expiration with the balloon-tipped catheter at steady state with the patient in a supine position. Measurements were based on an average of 5 cardiac cycles. Cardiac output was determined by the Fick or thermodilution method depending on the preference of the site (18). A low CO state was defined as systolic blood pressure <90 mm Hg and cardiac index (CI) <1.4 l/min/m^2 after the procedure (12).

Abbreviations and Acronyms

APS = acute procedural success
CI = cardiac index
CO = cardiac output
FSV = forward stroke volume
LA = left atrial/atrium
LV = left ventricular/ventricle
LVEDP = left ventricular end-diastolic pressure
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MR = mitral regurgitation
MV = mitral valve
NYHA = New York Heart Association
PA = pulmonary artery
PASP = pulmonary artery systolic pressure
PCWP = pulmonary capillary wedge pressure
PVR = pulmonary vascular resistance
RA = right atrial/atrium
SVR = systemic vascular resistance
TTE = transthoracic echocardiography

Table 1 Criteria for Moderate to Severe or Severe Mitral Regurgitation

Color flow jet may be central and large (>6 cm^2 or >30% of left atrial area) or smaller if eccentric and encircling the left atrium
Pulmonary vein flow may show systolic blunting or systolic flow reversal
Vena contracta width >0.3 cm measured in the parasternal long-axis view
Regurgitant volume >45 ml/beat
Regurgitant fraction >40%
Regurgitant orifice area >0.30 cm^2

Mitral regurgitation was classified as moderate to severe or severe if at least 3 of the above criteria were present and at least 1 of those 3 was quantitative (i.e., regurgitant volume, fraction, or orifice area).

Table 2 Baseline Patient Characteristics (n = 107)

Mean age, yrs	67 ± 14
Male	62%
Diabetes mellitus	21%
Hypertension	69%
Chronic obstructive pulmonary disease	12%
History of congestive heart failure	53%
Atrial fibrillation	29%
NYHA functional class	2.4 ± 0.7
NYHA functional class III/IV	46%
Tricuspid regurgitation	1.0 ± 0.5
Mitral regurgitation etiology	
Degenerative	84 (79%)
Ischemic/dilated	23 (21%)

Values are mean ± SD, %, or n (%).
NYHA = New York Heart Association.

Statistical analysis. Statistical analysis was performed with SPSS (version 18.0, SPSS Inc., Chicago, Illinois). Continuous variables are presented as means ± SD. Categoric data are presented as absolute numbers or percentages. Hemodynamic data before and following clip deployment were compared using paired *t* test. Between-group comparison was completed using independent *t* tests. The Levene's test was performed to assess homogeneity of variance. Chi-square test was used for comparison of categoric data. The p values were not adjusted for the multiple comparisons.

Results

We analyzed hemodynamic data from 107 patients. The patient demographic and baseline clinical data are shown in Table 2. New York Heart Association (NYHA) functional class III or IV symptoms were present in 46% of patients. Etiology of MR was degenerative in 84 (79%) and functional in 23 (21%) patients.

Figure 1 demonstrates a flow chart of patients with attempted MitraClip implantation. One or two MitraClips were implanted in 96 (90%) patients.

Effect of attempted MitraClip treatment on MR severity for the entire cohort (n = 107) for patients with (n = 96) and without (n = 11) clip implantation. For the entire study cohort (n = 107), MR grade decreased significantly from 3.3 ± 0.7 to 1.7 ± 0.9 ($p < 0.001$) and MR was reduced to ≤2+ in 79 (74%) patients (Tables 3 and 4).

Invasive hemodynamics for the entire cohort (n = 107). The CO increased from 5.0 ± 2.0 l/min to 5.76 ± 1.9 l/min ($p = 0.003$) and an increase in CI increased from 2.7 ± 1.0 l/min to 3.0 ± 1.0 l/min ($p = 0.003$) (Table 3). Improvement in CO and CI correlated with having a lower baseline CI prior to successful reduction in MR with the MitraClip ($r = 0.5$, $p < 0.001$). In patients with APS, mean systemic systolic arterial pressure increased from 109 ± 20 mm Hg to 113 ± 21 mm Hg ($p = 0.049$); however, diastolic and mean pressures remained unchanged. This hemodynamic response with an increase in mean CO and unchanged mean systemic arterial pressures resulted in a significant reduction in calculated systemic vascular resistance (SVR) from 1,253 ± 529 dyn·s/cm^5 to 1,058 ± 475 dyn·s/cm^5 ($p < 0.001$). The LVEDP decreased from 11.0 ± 8.6 mm Hg to 8.8 ± 6.0 mm Hg ($p = 0.016$), and RA pressure increased slightly from 8.31 ± 4.7 mm Hg to 9.3 ± 5.6 mm Hg ($p = 0.003$). There was no change in PASP, mean PCWP, and pulmonary vascular resistance (PVR). In addition, there was a nonsignificant opposite trend from 20.9 ± 12.8 l/min/m^2 to

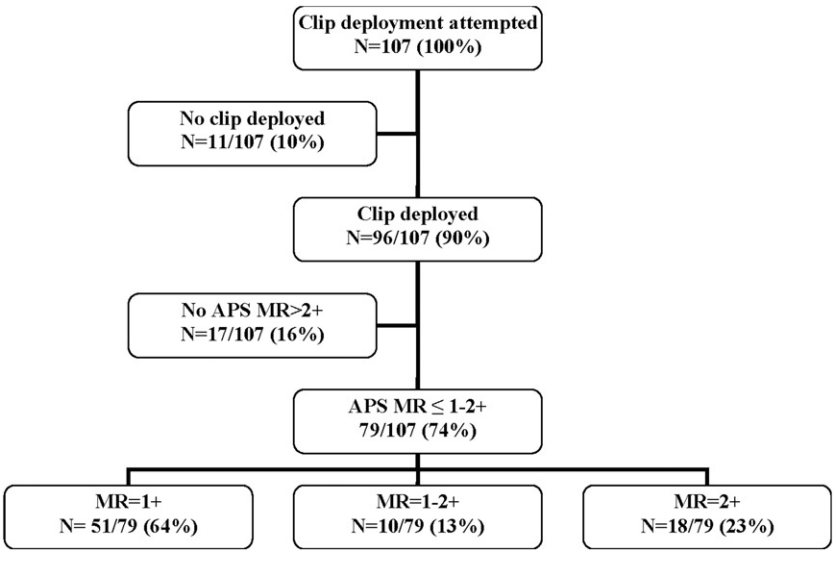

Figure 1 Flowchart Showing Results for 107 Study Patients

APS = acute procedural success; MR = mitral regurgitation.

Table 3 All Patients (N = 107)

	n	Pre	Post	p Value
Immediate invasive assessments				
Cardiac output	80	5.0 ± 2.0	5.6 ± 1.9	0.0033
Cardiac index	78	2.7 ± 1.0	3.0 ± 1.0	0.0025
LV peak systolic pressure	80	106.7 ± 23.5	105.2 ± 23.9	0.5541
LV end-diastolic pressure	79	11.0 ± 8.6	8.8 ± 6.0	0.0168
Atrial PCWP	76	16.7 ± 8.6	16.9 ± 7.3	0.813
Ventricular PCWP	77	20.9 ± 12.8	18.7 ± 8.5	0.0982
Mean PCWP	90	14.8 ± 6.2	14.9 ± 6.6	0.9307
PAP systole	92	34.4 ± 11.2	36.0 ± 10.5	0.1183
PAP diastole	91	14.9 ± 6.4	15.1 ± 6.0	0.7807
PAP mean	90	23.5 ± 11.2	23.8 ± 7.7	0.806
RAP	80	8.1 ± 4.7	9.3 ± 5.6	0.0278
SAP systole	92	108.9 ± 19.5	113.4 ± 20.9	0.0486
SAP diastole	92	57.6 ± 13.8	59.3 ± 12.6	0.2415
SAP mean	83	76.7 ± 14.5	78.4 ± 16.7	0.3515
Systemic vascular resistance	67	1,253 ± 529	1,058 ± 475	0.0008
Pulmonic vascular resistance	74	168 ± 229	153 ± 132	0.5992
Baseline vs. 24-h echo assessments				
MR grade	96	3.3 ± 0.7	1.7 ± 0.9	<0.0001
MR regurgitant volume	72	51.5 ± 20.4	29.8 ± 20.0	<0.0001
MR regurgitant fraction	72	45.9 ± 13.8	29.8 ± 15.5	<0.0001
LV ejection fraction (%)	90	59.8 ± 8.3	56.3 ± 9.4	<0.0001
Heart rate	81	69.5 ± 12.4	74.7 ± 11.7	0.0008
Forward stroke volume	82	57.2 ± 14.2	65.4 ± 17.7	<0.0001
Systolic arterial pressure	98	129 ± 21	120 ± 19	0.0001
Diastolic arterial pressure	98	73.8 ± 12.3	64.2 ± 13.0	<0.0001
LV end-diastolic volume	91	172 ± 37	158 ± 38	<0.0001
LV end-systolic volume	90	70.0 ± 24.8	70.6 ± 29.1	0.5992
LV end-diastolic diameter	87	5.54 ± 0.61	5.39 ± 0.62	0.0005
LV end-systolic diameter	91	3.48 ± 0.78	3.47 ± 0.77	0.9093

Values are mean ± SD.

LV = left ventricular; MR = mitral regurgitation; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SAP = systolic arterial pressure.

18.7 ± 8.5 mm Hg, p = 0.098). None of the study patients developed acute low CO state after transcatheter MV repair.

Noninvasive hemodynamics for the entire cohort (n = 107). TTE at discharge demonstrated an increase in FSV (57 ± 17 ml vs. 65 ± 18 ml, p < 0.001) and a reduction in regurgitant volume 52 ± 20 ml vs. 30 ± 20 ml, p < 0.001, and in RF 46 ± 14% vs. 30 ± 15%, p < 0.001. In addition, there was a reduction in LVEF (60 ± 8% vs. 56 ± 9%, p < 0.001) associated with a reduction in LVEDV (172 ± 37 ml vs. 158 ± 38 ml, p < 0.001), while there was no change in LVESV (p = NS).

Effect of clip implantation on MR severity (n = 96). Ninety six (90%) of the 107 patients who underwent implantation of a MitraClip experienced reduction of MR grade of the same magnitude as entire study cohort, in this group of patients with a MitraClip, MR grade reduced from 3.3 ± 0.7 l/min to 1.6 ± 0.8 l/min, p < 0.001.

Effect of MitraClip implantation on invasive hemodynamics (n = 96). There was an increase in CO from 5.0 ± 2.0 l/min to 5.6 ± 1.9 l/min, p = 0.003 and CI from 2.6 ± 1.0 l/min to 3.0 ± 1.0 l/min, p = 0.002, an increase in systemic systolic BP (109 ± 20 mm Hg vs. 114 ± 20 mm Hg, p = 0.034), and an associated reduction in SVR (1,259 ± 531 dyn·s/cm^5 vs. 1,059 ± 479 dyn·s/cm^5, p < 0.001). The LV EDP decreased (10.8 ± 8.8 vs. 8.8 ± 6.0 mm Hg, p = 0.026), while RA pressure increased (7.9 ± 4.7 mm Hg vs. 9.1 ± 5.7 mm Hg, p = 0.02). Similarly, there was a trend for reduction in the ventricular "v" wave of PCWP tracing from 20.1 ± 12.2 mm Hg to 17.9 ± 7.6 mm Hg, p = 0.098 and no significant change in the remainder of the hemodynamic variables.

Effect of MitraClip implantation on noninvasive hemodynamics (n = 96). By TTE, clip implantation resulted in increase in FSV from 58 ± 16 ml to 66 ± 18 ml, p < 0.001, a reduction in regurgitant volume from 51 ± 20 ml to 27 ± 17 ml, p < 0.001, and RF from 46 ± 14% to 28 ± 15%, p < 0.001. There was a reduction in LVEF from 60 ± 8% to 56 ± 9%, p < 0.001, associated with decrease in LVEDV from 171 ± 37 ml to 157 ± 37 ml, p < 0.001, while LVESV remained unchanged.

Comparison of hemodynamic and echo Doppler changes in patients with and without successful MitraClip treatment (n = 107). Eleven of 107 patients did not undergo placement of MitraClip. Most of the patients who did not receive a MitraClip did not have repeat hemodynamic measurements, thus, invasive hemodynamic data is only available from a small number of patients (3 patients and CO data

JACC Vol. 57, No. 16, 2011
April 19, 2011:1658–65

Table 4 Hemodynamic and Echo/Doppler Effects of MitraClip Therapy

	Clip Implant (n = 96)				No-Clip Implant (n = 11)			
	n	Pre Mean ± SD	Post Mean ± SD	p Value	n	Pre Mean ± SD	Post Mean ± SD	p Value
Immediate Invasive								
Cardiac output	79	5.0 ± 2.0	5.6 ± 1.9	0.0025	1	6.2 ± N/A	4.9 ± N/A	N/A
Cardiac index	77	2.6 ± 1.0	3.0 ± 1.0	0.0018	1	3.5 ± N/A	2.8 ± N/A	N/A
LV peak systolic pressure	77	107.1 ± 23.8	105.5 ± 24.0	0.5429	3	95.7 ± 13.4	96.7 ± 24.6	0.892
LV end-diastolic pressure	76	10.8 ± 8.8	8.8 ± 6.0	0.0263	3	14.3 ± 3.8	10.0 ± 5.3	0.2379
Atrial PCWP	73	16.3 ± 8.4	16.7 ± 7.3	0.5757	3	28.3 ± 6.0	22.7 ± 6.0	0.245
Ventricular PCWP	74	20.1 ± 12.2	17.9 ± 7.6	0.0981	3	40.3 ± 13.3	39.0 ± 5.0	0.8957
Mean PCWP	87	14.6 ± 6.1	14.6 ± 6.5	0.9914	3	22.7 ± 4.5	24.3 ± 2.5	0.671
PAP systole	87	33.8 ± 11.0	35.5 ± 10.3	0.0986	5	43.8 ± 11.7	44.6 ± 11.7	0.9297
PAP diastole	87	14.6 ± 6.3	14.9 ± 6.1	0.7111	4	20.8 ± 7.0	19.5 ± 2.1	0.7538
PAP mean	87	23.3 ± 11.3	23.4 ± 7.5	0.919	3	30.3 ± 2.5	35.7 ± 4.5	0.2556
RAP	76	7.9 ± 4.7	9.1 ± 5.7	0.0236	4	12.8 ± 3.3	12.5 ± 1.7	0.9157
SAP systole	88	109.1 ± 19.7	114.0 ± 20.4	0.0356	4	104.8 ± 12.8	100.0 ± 30.8	0.6862
SAP diastole	88	57.3 ± 13.9	59.1 ± 12.4	0.2284	4	65.3 ± 8.7	64.8 ± 17.3	0.943
SAP mean	80	76.5 ± 14.7	78.2 ± 16.0	0.3608	3	81.0 ± 7.2	83.7 ± 35.5	0.8892
Systemic vascular resistance	66	1,259 ± 531	1,059 ± 479	0.0006	1	865 ± N/A	1,045 ± N/A	N/A
Pulmonic vascular resistance	74	168 ± 229	153 ± 132	0.5992	0	N/A	N/A	N/A
24 h echo assessment								
MR grade	91	3.3 ± 0.7	1.6 ± 0.8	<0.0001	5	3.4 ± 0.55	3.4 ± 0.55	N/A
MR regurgitant volume	68	50.7 ± 20.1	27.4 ± 17.3	<0.0001	4	65.3 ± 23.9	72.0 ± 17.5	0.2088
MR regurgitant fraction	68	45.6 ± 14.1	28.3 ± 14.6	<0.0001	4	51.0 ± 9.1	54.5 ± 9.3	0.1402
LV ejection fraction (%)	86	59.9 ± 8.3	56.2 ± 9.6	<0.0001	4	58.5 ± 90.0	59.3 ± 5.6	0.7442
Heart rate	75	69.1 ± 11.4	74.4 ± 11.8	0.0007	6	74.5 ± 24.6	78.3 ± 10.4	0.637
Forward stroke volume	76	57.5 ± 15.6	66.3 ± 18.0	<0.0001	6	53.3 ± 6.8	53.9 ± 6.6	0.8195
Systolic arterial pressure	93	129 ± 21	121 ± 19	0.0004	5	121.2 ± 16.1	106.4 ± 8.7	0.1233
Diastolic arterial pressure	93	73.9 ± 12.4	64.8 ± 13.0	<0.0001	5	72.6 ± 11.9	52.8 ± 7.6	0.0122
LV end-diastolic volume	87	171 ± 37	157 ± 37	<0.0001	4	194 ± 35	182 ± 53	0.4092
LV end-systolic volume	86	69.5 ± 24.9	70.5 ± 29.5	0.4306	4	80.0 ± 22.2	73.0 ± 20.2	0.3551
LV end-diastolic diameter	83	5.54 ± 0.62	5.39 ± 0.61	0.0016	4	5.80 ± 0.36	5.40 ± 0.73	0.1449
LV end-systolic diameter	87	3.47 ± 0.79	3.48 ± 0.77	0.7598	4	3.63 ± 0.54	3.18 ± 0.65	0.078

Abbreviations as in Table 3.

from only 1 patient who did not receive a MitraClip). Similarly, echocardiographic stroke volume data was only available in 6 of 11 patients who did not undergo MitraClip procedure. As expected, MR grade did not change significantly in this subgroup of patients without the MitraClip (3.4 ± 0.55 vs. 3.4 ± 0.55, p = 1.0) and similarly, no significant change was noted in the FSV (51.0 ± 9.1 vs. 54.5 ± 9.3, p = 0.14) as well as LVEF (58.5 ± 90 vs. 59.3 ± 5.6, p = 0.74). The percent delta change in FSV did not reach statistical significance between the groups with the MitraClip vs. without MitraClip (18.2 ± 29% vs. 1.5 ± 11%, p = 0.168). No comparison between group changes was made for parameters if data was missing in majority of patients who did not receive MitraClip.

Discussion

This is the first study to document the acute hemodynamic effects of MitraClip treatment and of mechanical reduction of MR under beating-heart, closed-chest conditions in humans. Several important and unique findings were identified.

First, MitraClip treatment with a reduction of MR severity resulted in an increase in CO and FSV with concomitant reduction in SVR. Second, MitraClip treatment and reduction in MR grade resulted in favorable changes in LV loading conditions manifested by a decrease in LVEDP and LVEDV.

In chronic severe MR, high pre-load and reduced afterload (provided by low-impedance regurgitant flow into the left atrium) result in a high total CO. However, the magnitude of effective forward CO for any given myocardial contractility, LV pre-load, and heart rate has been thought to be primarily determined by the SVR. MitraClip treatment, which reduces the low-impedance mitral regurgitant flow into the left atrium, results in an immediate change in this relationship and leads to an increase in forward flow (CO, SV) and concomitant decrease in SVR, resulting in improvement or near normalization of CO.

Less invasive treatments such as the MitraClip therapy appear to be particularly beneficial in patients with an increased risk for developing a low CO state following MV surgery. Although surgical correction of MR has been used

successfully for 4 decades (20), it is commonly associated with a decrease in LV function and not infrequently an acute low CO state ensues (12). An acute low CO state in the immediate postoperative period is associated with an increased risk of death and major complications such as renal failure (10–13). Causes of diminished post-operative cardiac function following surgical MR correction have been associated with myocardial injury and depression of myocardial contractility owing to the use of cardiopulmonary bypass, cardioplegic arrest (21), and interruption of annular-chordal-papillary muscle continuity in nonvalve-sparing valve replacement (22–24). Over the last 40 years, several strategies have been implemented to decrease the prevalence of low CO syndrome, including revising the indications for MV surgery, with earlier intervention recommended even in the asymptomatic patient; improving cardioplegia solutions and myocardial protection; wider application of MV repair versus replacement; and subvalvular apparatus preservation whenever repair is not possible. Although the progress in operative care and surgical procedures have resulted in considerable improvement in peri-operative morbidity and mortality, the incidence of an acute CO state in selected subgroups of patients is as high as 12% to 19% (12,25). This risk is highest in elderly patients and in those with a history of congestive heart failure. In this trial of MV repair with the MitraClip system, no patient developed a peri-procedural low CO state. Moreover, 53% of our patients were age 70 years or older and 46% had advanced congestive heart failure symptoms (NYHA functional class III to IV). These findings suggest that closed-chest, off-pump MV repair on a beating heart carries a lower risk of developing a low CO state than previously reported with traditional MV repair and replacement surgery.

It has been argued that an additional mechanism of reduced LV systolic function following surgical MR reduction is the increase in afterload due to the elimination of the low-impedance regurgitant flow into the LA. However, the significance of this phenomenon has been controversial. Earlier publications have promulgated the concept of an acute increase in global LV afterload after MV replacement or repair as a cause of LV impairment (7,8), whereas some more recent reports have demonstrated that changes in afterload are not uniform and in fact that afterload in some patients may even decrease as a result of surgical correction of MR (26,27). We propose that the acute hemodynamic consequence of MR reduction is enhancement of FSV and CO and maintenance of mean arterial pressure while the changes seen in SVR are an adjustment to these hemodynamic changes.

The distinct effect of MitraClip treatment and its MR reduction on LV and LA hemodynamics are also intriguing. LVEDP and LVEDV after clip implantation fall, suggesting that the magnitude of reduction in regurgitant flow was substantial and sufficient to result in LV unloading.

Although reduction of regurgitant flow would be anticipated to have similar effects on LA and LV pressure there was no decrease in mean PCWP, and the PCWP "v" wave showed only a trend for reduction. The stability of the PCWP can be explained by the mild transmitral diastolic gradient associated with the creation of the double orifice valve. We previously reported that, following MitraClip treatment, the MV area was reduced from 6.0 ± 1.3 cm^2 to 3.6 ± 1.2 cm^2 and there is a small increase in the MV diastolic gradient from 1.7 ± 0.9 mm Hg to 4.1 ± 2.2 mm Hg by TTE Doppler (1.2 ± 6.8 days following MitraClip insertion) (28).

The LVEF decreased post-MitraClip by approximately 4 percentage points. This observation is not unique for MitraClip treatment as a reduction in LVEF of comparable magnitude is commonly observed following surgical treatment MR and is attributed to reduction of retrograde flow to the left atrium (29). Despite the reduction in total LVEF, the effective LVEF has increased as evidenced by an increase in forward stroke volume. Of note, the LVESV did not change, but LVEDV showed a statistically significant reduction, so that LVEF decreased slightly but not clinically significant. It is likely that the lack of change in the LVESV reflects preserved LV function and that LVEDV reduction is associated with the reduction in MR and consequently less transmitral flow filling the LV, resulting in a smaller LVEDV. The stroke volume goes up because more blood is ejected forward due to reduction in MR. The small rise in right atrial pressure may be related to intravenous hydration during the procedure, which is performed under general anesthesia. However, a contribution from the newly created left to right shunt after the transeptal puncture, which is requisite for this procedure, cannot be excluded.

The MitraClip therapy provides a unique model to study the acute hemodynamic changes secondary to MR reduction in isolation from the other changes that occur with open heart surgery. This allows for the assessment of the pure hemodynamic consequences of reduction of regurgitant flow. Patients who undergo the MitraClip procedure were not subjected to the hemodynamic insults related to thoracotomy, cardioplegic arrest and cardio-pulmonary bypass, well known to cause transient ventricular dysfunction and abnormal septal motion (30,31). Additionally surgery is often associated with major changes in loading conditions (32,33), rhythm disturbances (34,35), the use of vasoactive medications in the post-operative period, and post-operative bleeding.

Study limitations. All hemodynamic and CO data were obtained under general anesthesia before and after MitraClip placement. It is not possible to completely dissociate the effects of anesthesia from the effects of clip implantation on the hemodynamics. The role of intravenous hydration during this procedure on patients who had been fasting overnight and possibly became relatively hypovolemic at the beginning of the procedure is uncertain. It is, however, possible that in hypovolemic patients, intraprocedural intravenous hydration accounted in part for the rise in mean PCWP and systolic PA pressure following successful reduc-

tion in MR. Another limitation of this study is that stroke volume data was not available at the time of cardiac catheterization. Heart rate data for the purpose of the original EVEREST study were not required to be collected at the same time as determination of CO. Consequently, stroke volume could not be reliably calculated retrospectively from the nonsimultaneous CO and heart rate data. Therefore, the FSV data were obtained from the screening and pre-discharge TTE studies. However, it is reassuring that the effect of MitraClip treatment on FSV by the echo Doppler parameters and CO by thermo dilution or Ficks method are concordant. Namely, with post-MitraClip implantation, there is an increase in both CO and FSV.

Conclusions

The reduction in the regurgitant volume achieved by MitraClip treatment results in an acute augmentation in forward CO and FSV and maintenance of mean systemic arterial blood pressure. In addition, MitraClip treatment promotes LV unloading by reducing LVEDP and LVEDV. These hemodynamic effects are likely to reduce the risk of acute low CO state immediately after reduction in MR with the MitraClip device. These findings may have especially important implications for the use of the MitraClip therapy in patients with a high risk for a post-operative low CO state.

Reprint requests and correspondence: Dr. Robert J. Siegel, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 5623, Los Angeles, California 90048-1804. E-mail: siegel@cshs.org.

REFERENCES

1. Alfieri O, Maisano F, DeBonis M, et al. The edge-to-edge technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg 2001;122:674–81.
2. Maisano F, Torracca L, Oppizzi M, et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. Eur J Cardiothorac Surg 1998;13:240–5.
3. Maisano F, Schreuder JJ, Oppizzi M, Fiorani B, Fino C, Alfieri O. The double orifice technique as a standardized approach to treat mitral regurgitation due to severe myxomatous disease: surgical technique. Eur J Cardiothorac Surg 2000;17:201–15.
4. St. Goar FG, Fann JI, Komtebedde J, et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. Circulation 2003;108:1990–3.
5. Feldman T, Whitlow PL, Wasserman HS, et al. Significant reduction in mitral regurgitation twelve months following percutaneous mitral valve repair: initial experience with MitraClip device. Paper presented at: American College of Cardiology 56th Annual Scientific Session; March 24–27, 2007; New Orleans, LA.
6. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST phase I clinical trial. J Am Coll Cardiol 2005;46:2134–40.
7. Kouchoukos NT. Problems in mitral valve replacement. In: Kirklin JW, ed. Advances in Cardiovascular Surgery. New York, NY: Grune & Stratton, 1973:205–16.
8. Rankin JS, Nicholas LM, Kouchoukos NT. Experimental mitral regurgitation: effects on left ventricular function before and after elimination of chronic regurgitation in the dog. J Thorac Cardiovasc Surg 1975;70:478–88.
9. Rastelli GC, Kirklin JW. Hemodynamic state early after replacement of aortic valve with ball-valve prosthesis. Surgery 1967;61:873–9.
10. Appelbaum A, Kouchoukos NT, Blackstone EH, Kirklin JW. Early risks of open heart surgery for mitral valve disease. Am J Cardiol 1976;37:201–9.
11. Sethi GK, Miller DC, Souchek J, et al. Clinical, hemodynamic, and angiographic predictors of operative mortality in patients undergoing single valve replacement: Veterans Administration Cooperative Study on Valvular Heart Disease. J Thorac Cardiovasc Surg 1987;93:884–97.
12. Detaint D, Sundt TM, Nkomo VT, et al. Surgical correction of mitral regurgitation in the elderly: outcomes and recent improvements. Circulation 2006;114:265–72.
13. Christakis GT, Kormos RL, Weisel RD, et al. Morbidity and mortality in mitral valve surgery. Circulation 1985;72(3 Pt 2):II120–8.
14. Feldman T, Kar S, Rinaldi M, et al., EVEREST Investigators. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) Cohort. J Am Coll Cardiol 2009;54:686–94.
15. Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. Am J Cardiol 2007;100:1577–83.
16. Bonow RO, Carabello BA, Chaterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2006;48:e1–148.
17. Zoghbi WA, Enriquez-Sarano M, Foster E, et al., American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.
18. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJ. A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 1971;27:392–6.
19. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson LJ. Harrison's Principles of Internal Medicine. 16th edition. New York, NY: McGraw-Hill, 2005.
20. Remadi JP, Baron O, Roussel C, et al. Isolated mitral valve replacement with St. Jude medical prosthesis. Long-term results: a follow-up of 19 years. Circulation 2001;103:1542–5.
21. David TE, Burns RJ, Bacchus CM, Druck MN. Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae. J Thorac Cardiovasc Surg 1984;88:718–25.
22. Gaasch WH, Zile MR. Left ventricular function after surgical correction of chronic mitral regurgitation. Eur Heart J 1991;12 Suppl B:48–51.
23. Dilip D, Chandra A, Rajashekhar D, Padmanabhan M. Early beneficial effect of preservation of papillo-annular continuity in mitral valve replacement on left ventricular function. J Heart Valve Dis 2001;10:294–300.
24. Abu-Omar Y, Taggart DP. Off-pump coronary artery bypass grafting. Lancet 2002;360:327–30.
25. Tribouilloy CM, Enriquez-Sarano M, Schaff H, et al. Frye impact of preoperative symptoms on survival after surgical correction of organic mitral regurgitation: rationale for optimizing surgical indications. Circulation 1999;99:400–5.
26. Zile MR, Gaasch WH, Levine HJ. Left ventricular stress-dimension shortening relations before and after correction of chronic aortic and mitral regurgitation. Am J Cardiol 1985;56:99–105.
27. Goldfine H, Aurigemma GP, Zile MR, Gaasch WH. Left ventricular length-force-shortening relations before and after surgical correction of chronic mitral regurgitation. J Am Coll Cardiol 1998;31:180–5.
28. Hermann HC, Kar S, Siegel R, et al. Effectiveness of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. EuroIntervention 2009;4:437–42.
29. Enriquez-Sarano M, Tajik AJ, Schaff HV, et al. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol 1994;24:1536–43.
30. Yau TM, Fedak PW, Weisel RD, Teng C, Ivanov J. Predictors of operative risk for coronary bypass operations in patients with left ventricular dysfunction. J Thorac Cardiovasc Surg 1999;118:1006–13.

31. Vignola PA, Boucher CA, Curfman GD, et al. Abnormal interventricular septal motion following cardiac surgery: clinical, surgical, echocardiographic and radionuclide correlates. Am Heart J 1979;97:27–34.
32. Roberts AJ, Niarchos AP, Subramanian VA, et al. Systemic hypertension associated with coronary artery bypass surgery. Predisposing factors, hemodynamic characteristics, humoral profile, and treatment. J Thorac Cardiovasc Surg 1977;74:846–59.
33. Carrel T, Englberger L, Mohacsi P, Neidhart P, Schmidli J. Low systemic vascular resistance after cardiopulmonary bypass: incidence, etiology, and clinical importance. J Card Surg 2000;15:347–53.
34. Berdajs D, Schurr UP, Wagner A, Seifert B, Turina MI, Genoni M. Incidence and pathophysiology of atrioventricular block following mitral valve replacement and ring annuloplasty. Eur J Cardiothorac Surg 2008;34:55–61.
35. Echahidi N, Pibarot P, O'Hara G, Mathieu P. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol 2008;51:793–801.

Key Words: cardiac output ■ hemodynamics ■ MitraClip ■ mitral regurgitation.