Real-Time Left Ventricular Pressure-Volume Loops During Percutaneous Mitral Valve Repair With the MitraClip System

Oliver Gaemperli, MD*; Patric Biaggi, MD*; Remo Gugelmann; Martin Osranek, MD; Jan J. Schreuder, MD, PhD; Ines Bühler; Daniel Sürder, MD; Thomas F. Lüscher, MD; Christian Felix, MD; Dominique Bettex, MD; Jürg Grünenfelder, MD; Roberto Corti, MD

Background—Percutaneous mitral valve repair with the MitraClip device has emerged as an alternative to surgery for treating severe mitral regurgitation. However, its effects on left ventricular loading conditions and contractility have not been investigated yet.

Methods and Results—Pressure-volume loops were recorded throughout the MitraClip procedure using conductance catheter in 33 patients (mean age, 78±10 years) with functional (45%), degenerative (48%), or mixed (6%) mitral regurgitation. Percutaneous mitral valve repair increased end-systolic wall stress (WSₚₛ; from [median] 184 mm Hg [interquartile range (IQR), 140–200 mm Hg] to 209 mm Hg [IQR, 176–232 mm Hg]; P=0.001) and decreased end-diastolic WS (WSₚₑ, from 48 mm Hg [IQR, 28–58 mm Hg] to 34 mm Hg [IQR, 21–46 mm Hg]; P=0.005), whereas the end-systolic pressure-volume relationship was not significantly affected. Conversely, cardiac index increased (from 2.6 L·min⁻¹·m⁻² [IQR, 2.2–3.0 L·min⁻¹·m⁻²] to 3.2 L·min⁻¹·m⁻² [IQR, 2.6–3.8 L·min⁻¹·m⁻²]; P<0.001) and mean pulmonary capillary wedge pressure decreased (from 15 mm Hg [IQR, 12–20 mm Hg] to 12 mm Hg [IQR, 10–13 mm Hg]; P<0.001). Although changes in WSₚₑ were not correlated with changes in cardiac index, changes in WSₚₑ correlated significantly with changes in mean pulmonary capillary wedge pressure (r=0.63, P<0.001). Total mechanical energy assessed by the pressure-volume area remained unchanged, resulting in a more favorable index of forward output (cardiac index) to mechanical energy (pressure-volume area) after mitral valve repair. On follow-up (153±94 days), New York Heart Association functional class was reduced from 2.9±0.6 to 1.9±0.5 (P<0.001) at 3 months, and echocardiographic follow-up documented a stepwise reduction in end-diastolic volume (from 147 mL [IQR, 95–191 mL] to 127 mL [IQR, 82–202 mL]; P=0.036).

Conclusions—Percutaneous mitral valve repair improves hemodynamic profiles and induces reverse left ventricular remodeling by reducing left ventricular preload while preserving contractility. In nonsurgical candidates with compromised left ventricular function, MitraClip therapy could be considered an alternative to surgical mitral valve repair.

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Key Words: catheters ■ hemodynamics ■ mitral valve annuloplasty ■ mitral valve insufficiency ■ pressure-volume loops

A novel percutaneous method for mitral valve repair (MVR) has recently been developed.1 Conceptually, this technique is based on the surgical method developed by Alfieri, which consists of edge-to-edge approximation of the middle scallops of the mitral valve leaflets by percutaneous delivery of a mitral clip, thereby creating a double-orifice mitral valve.2 As a result of promising initial clinical experiences with percutaneous edge-to-edge MVR,3–7 the MitraClip device has been implanted in >6000 patients worldwide. However, data on the hemodynamic consequences of percutaneous MVR are scarce,8,9 and its effect on left ventricular (LV) preload, afterload, and contractility, the main determinants of LV pump performance, are yet to be investigated.

Clinical Perspective on p 1027

Simultaneous in vivo pressure-volume (PV) measurements with a conductance catheter (CC) placed in the LV allow real-time assessment of the LV PV relationship.10 In fact, percutaneous MVR provides a unique pathophysiological model for assessing the immediate hemodynamic effects of MR reduction on LV performance, eliminating any confounding factors from cardiopulmonary bypass or chordal ablation. Preliminary experiences suggest that despite an initial slight
decrease in LV ejection fraction, percutaneous edge-to-edge MVR did not negatively affect cardiac output, and so far, no reports of acute low-output states after MVR have been published, even in patients with markedly compromised LV function. However, the mechanisms by which percutaneous edge-to-edge MVR may influence LV pump performance and affect LV preload, afterload, and contractility are still to be determined.

Thus, the purposes of this study were to investigate the immediate changes in LV PV relationships during percutaneous edge-to-edge MVR with the MitraClip device using a CC and to relate these findings to acute hemodynamic changes and midterm clinical outcomes.

Methods

Patient Population and Study Design

We included consecutive patients undergoing percutaneous MVR with the MitraClip system at the University Hospital Zurich, Zurich, Switzerland. Patients were selected for the procedure if they had moderate to severe (3+) or severe (4+) mitral regurgitation (MR), and met Class I or IIa recommendations for mitral valve surgery according to current guidelines, and were considered high risk for surgery. Each subject’s eligibility for percutaneous MVR was discussed by an interdisciplinary heart valve team that included an interventional cardiologist, a cardiac surgeon, an echocardiographer, and a cardiac anesthetist. Exclusion criteria were rheumatic heart disease, endocarditis, mitral valve orifice area ≤ 2.0 cm², extensive prolapse of flail leaflets (prolapse width > 25 mm, flail gap > 20 mm), or any interventional or surgical procedure within 30 days of the index procedure. All patients gave written informed consent to be included in a prospective MitraClip registry (MitraSwiss registry). The protocol of the MitraSwiss registry includes invasive hemodynamic data collection through catheterization of the left- and right-sided chambers of the heart and was approved by the local institutional review board.

MVR Procedure

Percutaneous MVR with the MitraClip device (Abbott Vascular, Menlo Park, CA) was performed according to standard technique described elsewhere with echocardiographic (3-dimensional transesophageal echocardiography) and fluoroscopic guidance. General anesthesia was established with a continuous infusion of intravenous propofol and remifentanil, and patients were ventilated routinely with an inspiratory oxygen fraction (FiO2) of 60% to 80%, which was maintained over the entire duration of the procedure. Acute procedural success was defined as successful MitraClip implantation with MR reduction to grade 2+ or less by echocardiography.

Instrumentation

Simultaneous LV PV measurements were performed with a CC (CD Leycom, Zoetermeer, the Netherlands). This catheter is a pigtail-shaped central-lumen 7F flexible catheter that is placed in the LV via a 0.025-in J-tipped guidewire. It contains a solid-state pressure sensor and 12 electrodes situated at regular intervals along the catheter and is connected to a PV signal processor (Inca, CD Leycom). The conductance method calculates continuous LV volume tracings by measuring parallel electric conductance between adjacent electrodes, and it has been successfully validated against cine computed tomography and electroconductive balloons in animals. The correct position of the CC was verified by fluoroscopy and by inspection of the segmental conductance signals. Arterial oxygen saturation was obtained from the distal catheter lumen. Volume calibration was performed by LV volumes from transthoracic 3-dimensional echocardiography (obtained under general anesthesia in the operating room immediately before the start of the procedure).

PV loops were recorded during steady-state conditions before and after MitraClip implantation, avoiding excessive arrhythmia from premature beats. Recorded variables were averaged from several heartbeats (at least 10 seconds for sinus rhythm or at least 15 seconds in atrial fibrillation) to minimize inaccuracies from beat-to-beat variations and changes in venous return resulting from mechanical ventilation. In a subgroup of 31 patients, a repeat baseline recording was performed to assess the reproducibility of CC measurements.

Catheterization of the right side of the heart was performed with a 6F single-lumen balloon-tipped flow-directed Swan-Ganz catheter (Arrow International, Inc, Reading, PA) to measure mean pulmonary capillary wedge pressure (PCWP), and pulmonary artery pressure, pulmonary artery oxygen saturation, and right atrial pressure. Left atrial pressure was measured through the transseptal sheath. All hemodynamic measurements were conducted during the index MVR procedure before MitraClip implantation and were repeated immediately after deployment of the last clip.

Variables and Data Analysis

CC data analysis was performed with dedicated data acquisition and analysis software (Conduct NT, version 3.18.1, CD Leycom) by consensus of 2 readers unaware of the clinical history and the success of the MVR procedure. In addition to instantaneous LV volumes and pressure, this software calculates load-independent parameters of LV contractility. The end-systolic PV relationship (ESPVR) represents the ratio of LV pressure to LV volume at the end of ventricular systole (uppermost left corner of the PV loop). The Starling contractile index (SCI) is calculated as the maximal rate of pressure change over time during isovolumetric contraction (dP/dtmax) normalized to end-diastolic volume (EDV). The (external) stroke work (eSW) was calculated as the area within the PV loop and normalized to EDV to obtain preload-recruitable stroke work (PRSW). PV area (PVA), a measure of total mechanical energy generated by ventricular contraction, was calculated as the sum of eSW and elastic potential energy according to the following equation:

\[
PVA = eSW + 0.5 \times ESP^2/ESPVR
\]

LV preload and afterload were estimated from end-diastolic (WSED) and end-systolic (WSES) wall stress, respectively, which were calculated according to the following equation for time-dependent WS:

\[
WS(t) = P(t) \times [1 + 3 \times V(t)/V_{max}]
\]

where WS(t) is LV WS, P(t) is LV pressure, and V(t) is LV volume at a given time point throughout the cardiac cycle. This equation assumes that WS is fairly uniform throughout the ventricular wall and is relatively independent of the geometry of the LV. LV wall volume (V_{wall}) was calculated according to the cube function formula, which approximates the shape of the LV as a prolate ellipsoid of regular configuration and a ratio of long- to short-axis length of 2.15:

\[
V_{wall} = 0.8 \times \left[ (IVST_t + PWT_d + EDD)^3 - EDD^3 \right]
\]

where IVST_t is the diastolic thickness of the interventricular septum, PWT_d is the diastolic posterior wall thickness, and EDD is the end-diastolic diameter measured on M-mode echocardiography.

Cardiac output and cardiac index (CI) were calculated with the Fick method. Systemic vascular resistance and pulmonary vascular resistance were calculated as the ratio between the pressure drop along the vascular bed and the cardiac output and converted to metric units (dynes·s·cm⁻⁵).

Clinical and Echocardiographic Follow-up

Clinical follow-up was obtained from follow-up visits, in-hospital records, and/or direct interview of the patient or his/her general practitioner. Clinical end points included death, recurrent hospitalization for congestive heart failure, mitral valve surgery, and New York Heart Association functional class.
LV volumes at follow-up were assessed from 2-dimensional transthoracic echocardiography using the area-length method, and systolic pulmonary pressure was estimated from peak tricuspid regurgitant jet velocity by use of the Bernoulli equation.

Statistical Analysis
Statistical analysis was performed with the SPSS software package (SPSS 12.0.1 for Windows, SPSS Corp). Quantitative data are expressed as mean±SD or median with interquartile range (IQR) when appropriate, and categorical data are given in proportions and percentages. Statistical comparisons of quantitative data were performed with a 2-tailed Wilcoxon signed-rank test for paired samples. The Friedman test was used for repeated measurements of LV volumes. Categorical data were compared by use of the Fisher exact test. Results from different measurements were correlated with the Spearman method. Reproducibility of PV measurements was tested by the use of linear regression and Bland-Altman limits of agreement. The reproducibility coefficient was calculated as 1.96 times the SD of the differences, as proposed by Bland and Altman. A value of P<0.05 was considered statistically significant for all tests.

Results
Patient Population
Of 37 consecutive patients undergoing percutaneous MVR, hemodynamic data and PV loops were obtained in 33 patients. In 4 patients, technical problems, catheter malfunction, or inadvertent catheter dislodgement hindered successful data recording. The patients’ baseline characteristics are shown in Table 1. The type of MR was degenerative (DMR) in 16 patients (48%), functional (FMR) in 15 patients (45%), and mixed in 2 patients (6%). MR severity at baseline was 3+ in 7 patients (21%) and 4+ in 26 patients (79%). Three patients had previously undergone surgical MVR with ring annuloplasty (n=2) or Alfieri stitch (n=1).

Procedural Outcome
MitraClip implantation was successful in 31 of 33 patients (acute procedural success rate, 94%) with an average of 1.9 implanted clips per patient (1 clip in 7 patients, 2 clips in 21 patients, 3 clips in 4 patients, and 4 clips in 1 patient). The procedure failed in 2 patients because of excessive posterior annular calcification with poor echocardiographic image quality (n=1) or partial clip detachment (n=1). Postinterventional complication rates were low, and there were no in-hospital deaths. Two patients required vasopressor therapy over 1 to 3 days after the procedure, but none had intra-aortic balloon counterpulsation.

Hemodynamic Data
All hemodynamic variables were obtained under general anesthesia before and immediately after the MitraClip procedure and are summarized in Table 2. Percutaneous MVR significantly reduced LV end-diastolic pressure and mean pulmonary artery pressure by (median) 3 mm Hg, mean PCWP by 5 mm Hg, and PCWP v-wave by 7 mm Hg, whereas mean arterial pressure was increased by 9 mm Hg. EDV remained unchanged, whereas end-systolic volume increased by 11 mL after MVR (P=0.006). This resulted in a reduction of ejection fraction (EF) from 55% (IQR, 45% to 65%) to 42% (IQR, 31% to 56%; P<0.001). Nonetheless, cardiac output and CI increased significantly by 0.9 L/min and 0.5 L-min⁻¹m⁻², respectively (Figure 1). There was no significant correlation between changes in EF and changes in CI during percutaneous MVR (r=−0.33, P=0.06).

Afterload, Preload, and LV Contractility
Percutaneous MVR increased WSES by 30 mm Hg (P=0.001) and lowered WSED by 8 mm Hg (P=0.005; Table 2). However, no significant changes were observed for SCI and ESPVR (Figure 1). After percutaneous MVR, PRSW decreased by 3 mm Hg (P=0.001).

Table 1. Baseline Characteristics (n=33)

<table>
<thead>
<tr>
<th>Age, y</th>
<th>78±10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>14 (42)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25±4</td>
</tr>
<tr>
<td>Clinical features, n (%)</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>21 (64)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>12 (36)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>14 (42)</td>
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<tr>
<td>Previous MI</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Previous mitral valve surgery</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15 (45)</td>
</tr>
<tr>
<td>COPD</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4 (12)</td>
</tr>
<tr>
<td>Impaired renal function (eGFR &lt;60 mL/min)</td>
<td>20 (61)</td>
</tr>
<tr>
<td>Cancer</td>
<td>4 (12)</td>
</tr>
<tr>
<td>NYHA functional class, n (%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8 (24)</td>
</tr>
<tr>
<td>III</td>
<td>20 (61)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (15)</td>
</tr>
<tr>
<td>STS mortality score</td>
<td>6±5</td>
</tr>
<tr>
<td>STS mortality and morbidity score</td>
<td>27±12</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and STS, Society of Thoracic Surgeons. Data are given as mean±SD unless otherwise stated.
Table 2. Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Before MitraClip</th>
<th>After MitraClip</th>
<th>Median Difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pressures and volumes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDV, mL</td>
<td>147 (106 to 183)</td>
<td>138 (104 to 185)</td>
<td>−9 (−21 to 5)</td>
<td>0.18</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>57 (39 to 112)</td>
<td>84 (43 to 118)</td>
<td>11 (0 to 25)</td>
<td>0.006</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>14 (11 to 17)</td>
<td>11 (8 to 14)</td>
<td>−3 (−4 to 0)</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>64 (56 to 72)</td>
<td>68 (60 to 77)</td>
<td>9 (0 to 14)</td>
<td>0.02</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>28 (24 to 32)</td>
<td>25 (22 to 29)</td>
<td>−3 (−5 to 0)</td>
<td>0.001</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>15 (12 to 20)</td>
<td>12 (10 to 13)</td>
<td>−5 (−8 to −2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vPCWP, mm Hg</td>
<td>22 (16 to 30)</td>
<td>14 (13 to 16)</td>
<td>−7 (−18 to −2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mLAP, mm Hg</td>
<td>15 (10 to 21)</td>
<td>11 (9 to 14)</td>
<td>−3 (−7 to 0)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Afterload and preload</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSES, mm Hg</td>
<td>184 (140 to 200)</td>
<td>209 (176 to 232)</td>
<td>30 (10 to 58)</td>
<td>0.001</td>
</tr>
<tr>
<td>WSED, mm Hg</td>
<td>48 (28 to 58)</td>
<td>34 (21 to 46)</td>
<td>−8 (−19 to 2)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Load-independent parameters of LV contractility</strong></td>
<td></td>
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<tr>
<td>SCI, mm Hg·mL−1·s−1</td>
<td>4.8 (3.1 to 8.9)</td>
<td>5.8 (3.7 to 9.2)</td>
<td>0.2 (−0.5 to 1)</td>
<td>0.23</td>
</tr>
<tr>
<td>ESPVR, mm Hg/mL</td>
<td>1.6 (0.7 to 2.6)</td>
<td>1.2 (0.8 to 2.1)</td>
<td>−0.1 (−0.3 to 0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>PRSW, mm Hg</td>
<td>41 (29 to 60)</td>
<td>30 (24 to 52)</td>
<td>−3 (−13 to 1)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LV myocardial energetics</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>eSW, mm Hg·mL</td>
<td>6357 (3756 to 7671)</td>
<td>4490 (2957 to 6754)</td>
<td>−579 (−2287 to 228)</td>
<td>0.004</td>
</tr>
<tr>
<td>PVA, mm Hg·mL</td>
<td>9169 (6691 to 12 033)</td>
<td>8634 (6951 to 10 717)</td>
<td>−52 (−1937 to 1181)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Cl indicates cardiac index; CO, cardiac output; EDP, end-diastolic pressure; EDV, end-diastolic volume; ESPVR, end-systolic pressure-volume relationship; LV, left ventricular; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; mLAP, mean left atrial pressure; PRSW, preload-recruitable stroke work; PVA, pressure-volume area; PVR, pulmonary vascular resistance; SCI, Starling contractile index; SVR, systemic vascular resistance; vPCWP, pulmonary capillary wedge pressure v-wave; WS ES, end-systolic wall stress; and WS ED, end-systolic wall stress. All values are given as median (interquartile range).

LV Myocardial Energetics

Percutaneous MVR decreased eSW (Table 2) but increased potential energy (from 2769 mm Hg·mL [IQR, 1796–4763 mm Hg·mL] to 3921 mm Hg·mL [IQR, 2221–5474 mm Hg·mL]; P=0.001). As a result, PVA remained unchanged. The ratio of forward cardiac output to PVA (multiplied by heart rate to account for 1 minute of PVA) increased significantly after MitraClip implantation from 0.0084 mm Hg−1 (IQR, 0.0065–0.0106 mm Hg−1) to 0.0091 mm Hg−1 (IQR, 0.0082–0.0145 mm Hg−1; P=0.007; Figure 4).

Comparison Between DMR and FMR

Table 3 shows a comparison of hemodynamics and CC data for DMR (n=16) and predominantly FMR (functional plus mixed, n=17). There was a similar reduction in mean pulmonary artery pressure and mean PCWP in both groups; however, the decreases in end-diastolic pressure and WSES, and the increase in CI were larger in the DMR group (P<0.05). Notably, changes in WSES were similar in both groups with no excess afterload increase in the FMR group. Interestingly, changes in ESPVR and PRSW appeared more favorable for FMR, whereas for SCI, no significant differences were found between the groups (Table 3). Individual changes in hemodynamic parameters are displayed for DMR and FMR patients in Figure 5.

Reproducibility of CC Measurements

Reproducibility of measurements and derived values with the CC was good with the following correlation coefficients: EDV, r=0.97; end-systolic volume, r=0.96; end-diastolic pressure, r=0.86; PRSW, r=0.96; SCI, r=0.96; ESPVR, r=0.81; WSES, r=0.80; and WSED, r=0.86 (P<0.001 for all). Bland-Altman limits of agreement were narrow with the following reproducibility coefficient (given in percent of the average value): EDV, 26%; end-systolic volume, 52%; end-diastolic pressure, 32%; PRSW, 31%; SCI, 38%; ESPVR, 32%; and WSED, 39%, except for ESPVR, which had larger variability (109%). There was no significant bias.

Clinical and Echocardiographic Follow-up

During a follow-up period of 153±94 days, 5 patients (15%) died and 4 patients (12%) were readmitted for congestive heart failure. New York Heart Association functional class decreased from 2.9±0.6 to 1.9±0.5 (P<0.001) at 3 months. Echocardiographic follow-up was available in 22 patients at 69±48 days after the index procedure. MR severity was 1+ in
contractility measured by load-independent parameters is an acute decline in EF after the MVR procedure, LV the potentially negative afterload increase. Second, despite the beneficial effect of end-diastolic unloading outweighs output and decrease in pulmonary pressure indicate that preload. However, the significant increase in forward cardiac results in an acute increase in LV afterload and a reduction in summary as follows: First, successful percutaneous MVR with the MitraClip on LV performance (including LV contractility, afterload, and preload) as assessed by CC and their relationship to hemodynamic (including LV contractility, afterload, and preload) as assessed by CC and their relationship to hemodynamic changes and clinical outcomes. Our results can be summarized as follows: First, successful percutaneous MVR results in an acute increase in LV afterload and a reduction in preload. However, the significant increase in forward cardiac output and decrease in pulmonary pressure indicate that the beneficial effect of end-diastolic unloading outweighs the potentially negative afterload increase. Second, despite an acute decline in EF after the MVR procedure, LV contractility measured by load-independent parameters is not significantly affected. Third, total mechanical energy (PVA) remains unchanged; therefore, myocardial oxygen consumption is not expected to increase after MVR. Fourth, these beneficial hemodynamic changes, combined with a preserved LV contractility, appear to reverse LV remodeling by reducing EDV and are associated with an improvement in functional status.

Changes in LV Loading Conditions
Surgical observations have raised the concern that removing the low-impedance regurgitant flow into the left atrium may abruptly impair LV performance, resulting in an acute postoperative low-output state. However, these observations are confounded by factors such as changes in LV geometry induced by chordal ablation and extracorporeal circulation, both of which may underlie deterioration of LV contractility. We observed a significant 21% increase in LV afterload (estimated from WSes) after percutaneous MVR, which likely contributes to the acute decline in LV EF observed after MVR. The reduction in the regurgitant fraction decreases systolic offloading by occluding the low-impedance left atrial pathway. However, in our study population, a large increase in systolic load did not predict low cardiac output after MVR (Figure 2A). Conversely, a significant 17% reduction in LV preload could be observed. This effect of diastolic LV unloading was associated with a reduction in pulmonary pressures (Figure 2B). Therefore, the beneficial effect of diastolic LV unloading appears to outweigh the potentially negative afterload...
increase. An acute decrease in LV afterload in heart failure patients by intra-aortic balloon pumping has been shown to induce acute leftward shifts of the LV PV plane along the patient’s end-systolic elastance curve, resulting in an acute increase in stroke volume and a concomitant decrease in preload. Conversely, it can be expected that decreasing the LV offloading effects of MR will acutely increase the afterload along the patient’s end-systolic elastance.

Contrary to the general notion, afterload tends to be high in chronic MR as a result of progressive ventricular enlargement, particularly in the decompensated stage. Thus, an uncontrolled increase in LV afterload, also called afterload excess, is an important concern after MR correction because it may lead to further deterioration of LV function. Several studies have documented a significant increase in systolic LV load after successful mitral valve surgery in patients with chronic decompensated MR but not in the chronic compensated stage. It may well be that some of our patients were in the chronic decompensated stage, which would explain the increase in afterload. However, an important difference from previously mentioned studies is that we assessed cardiac loading conditions immediately (ie, minutes) after correction of the MR, whereas others used echocardiographic assessment several days after surgery, allowing early LV remodeling to take place.

Compared with patients with DMR, the reduction in LV preload (measured by end-diastolic pressure and WS_Ed) and increase in CI were significantly lower in FMR patients. These differences in ventricular unloading after MVR in DMR versus FMR patients can be explained by fundamentally different pathophysiologic mechanisms underlying the
origin of heart failure in these 2 subgroups. In DMR, the
effect of MR on the LV is predominantly volume overload,
which can be effectively reversed by reducing or abolishing

Table 3. Hemodynamic Variables Before and After Mitral Valve Repair According to Mitral Regurgitation Type

<table>
<thead>
<tr>
<th></th>
<th>Degenerative (n=16)</th>
<th>Nondegenerative (Functional + Mixed) (n=17)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After MVR</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>14 (10 to 18)</td>
<td>9 (7 to 12)</td>
</tr>
<tr>
<td>mPAP, mm Hg</td>
<td>28 (24 to 34)</td>
<td>26 (22 to 32)</td>
</tr>
<tr>
<td>mPCWP, mm Hg</td>
<td>19 (13 to 22)</td>
<td>12 (9 to 13)</td>
</tr>
<tr>
<td>WS_{es}, mm Hg</td>
<td>149 (130 to 189)</td>
<td>185 (150 to 212)</td>
</tr>
<tr>
<td>WS_{es}, mm Hg</td>
<td>40 (25 to 57)</td>
<td>25 (18 to 34)</td>
</tr>
<tr>
<td>SCI, mm Hg/mL</td>
<td>7.9 (6.4 to 10.8)</td>
<td>9.1 (5.9 to 10.7)</td>
</tr>
<tr>
<td>ESPVR, mm Hg/mL</td>
<td>2.2 (1.7 to 3.7)</td>
<td>2.0 (1.1 to 2.9)</td>
</tr>
<tr>
<td>PRSW, mm Hg</td>
<td>54 (44 to 67)</td>
<td>43 (29 to 58)</td>
</tr>
<tr>
<td>eSW, mm Hg/mL</td>
<td>6470 (4530 to 7651)</td>
<td>4479 (2992 to 3326)</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>2.6 (2.3 to 3.7)</td>
<td>3.7 (2.7 to 5.2)</td>
</tr>
</tbody>
</table>

CI indicates cardiac index; EDP, end-diastolic pressure; ESPVR, end-systolic pressure-volume relationship; eSW, external stroke work; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; MVR, mitral valve repair; PRSW, preload-recruitable stroke work; SCI, Starling contractile index; WS_{es}, end-diastolic wall stress; and WS_{es}, end-systolic wall stress.

*P value for comparison of relative changes between groups.
†P<0.05 for between-group comparisons of baseline variables.
‡P<0.05 for between-group comparisons of postprocedural variables.

origin of heart failure in these 2 subgroups. In DMR, the
effect of MR on the LV is predominantly volume overload,
which can be effectively reversed by reducing or abolishing

Figure 5. Individual changes in hemodynamic and conductance catheter parameters according to type of mitral regurgitation (MR): black, degenerative MR; blue: functional MR. Box plots show median (thick lines), quartiles (upper and lower box boundaries), and extreme values (whiskers). EDP indicates end-diastolic pressure; ESPVR, end-systolic pressure-volume relationship; mPCWP, mean pulmonary capillary wedge pressure; and WS_{es}, end-systolic wall stress.

However, in FMR, the pathophysiology of heart fail-
ure is more complex and involves reduced contractility as a
result of ischemic or dilated cardiomyopathy. Hence, in this
LV contractility. Interestingly, changes in load-independent parameters appeared even more favorable in our group of patients with FMR (with even a 7% increase in SCI and ESPVR) compared with DMR (Table 3). Thus, percutaneous MVR with the MitraClip device appears to spare LV contractility and therefore may still be considered a valuable treatment option for chronic FMR in patients with poor ventricular contractility. On the other hand, percutaneous MVR does not eliminate MR in all patients, which may contribute to poor outcomes in a subset of patients.

**Effect of Percutaneous MVR on LV Energetics**

Percutaneous MVR resulted in an energy transfer from eSW to potential energy. This shift represents a loss of efficiency in the transfer of energy from the PVA to external mechanical work (eSW) and was described earlier as a physiological response to an abrupt increase in afterload in experimental animal models. However, net total mechanical energy measured by the PVA (the main determinant of myocardial oxygen consumption) remained unchanged after MVR. Thus, the ratio of forward cardiac output to PVA (multiplied by heart rate) increased significantly by a median of 23%. This indicates that percutaneous MVR may improve forward cardiac output by approximately one fourth for a given unit of total mechanical energy (PVA) and hence myocardial oxygen consumption. This may be a particularly attractive feature in patients with ischemic cardiomyopathy in whom myocardial oxygen delivery may be compromised and therefore an increased oxygen demand could lead to significant myocardial ischemia.

**Relationship of CC Measurements and Hemodynamic Changes to Clinical and Echocardiographic Outcomes**

Although LV volumes do not decrease immediately after MVR, there is a downward trend in the first months after the procedure, with a decrease in EDV indicating a favorable reverse LV remodeling. This reverse remodeling may be a result of improved hemodynamic conditions from removing (or reducing) MR (ie, lower LV filling pressures, improved CI) combined with a sparing of LV contractility. Notably, low-contractility parameters at baseline did not predict adverse LV remodeling on follow-up. The reduction of systolic pulmonary pressures on echocardiography suggests a sustained improvement of loading conditions over the ensuing months after percutaneous MVR.

There is evidence from prior work that the salutary hemodynamic changes elicited by percutaneous MVR translate into improved clinical outcomes. Nonetheless, despite the short follow-up, event rates (death, readmission for congestive heart failure) were considerable, given the substantial comorbid status of our patients. However, the limited number of subjects and the lack of a control group preclude any firm conclusion about the relationship of the observed hemodynamic changes with any potential clinical benefit. A recent nonrandomized study documented superiority of percutaneous MVR over medical treatment in patients with predominantly FMR, indicating that despite high event rates, percutaneous MVR still offers a clinical benefit over medical treatment. Nonetheless, larger prospective, randomized trials are eagerly awaited to confirm this hypothesis.
Limitations
We acknowledge a limited sample size. Additionally, a large number of statistical tests were performed without correction for multiplicity. However, given the novelty of the percutaneous MVR technique and the complexity of intraprocedural CC measurements, the sample size appeared reasonable to reach clinically meaningful conclusions. We cannot exclude a potential influence of intraprocedural fluctuations in catheter positioning, temperature, blood viscosity, and/or salinity on parallel conductance, affecting estimations of LV volumes measured by CC. However, given the percutaneous nature of the procedure, loss of blood and electrolytes was limited and therefore unlikely to play a significant confounding role.

We did not measure end-systolic elastance (ie, the slope of the ESPVR, a load-independent index of LV contractility) because doing so generally requires an intervention such as inflation of an occlusive balloon in the inferior vena cava.

Finally, by the very nature of the procedure, all measurements were acquired during general anesthesia, which is known to underestimate loading conditions compared with the conscious nonseated state. Therefore, absolute values for preload, afterload, and contractility parameters may be different in the conscious state. Additionally, hyperoxygenation resulted in higher mixed venous oxygen saturations and consequently higher values for cardiac output and CI calculated by the Fick method than would be expected for this population. Finally, assumptions about resting oxygen consumption do not necessarily apply to the anesthetized patient and are a further limitation of the Fick principle. However, because preprocedural and postprocedural measurements were obtained under the same conditions, the relative changes in the latter parameters are expected to represent true changes.

Clinical Implications
Despite significant morbidity and mortality, many patients with severe MR are denied surgery because of a high surgical risk and poor outcomes. Percutaneous MVR with the MitraClip system represents a novel and promising treatment alternative in nonsurgical candidates. The present study demonstrates that by preserving LV contractility, reducing regurgitant mitral flow, and lowering LV preload, percutaneous MVR may have beneficial hemodynamic effects. Larger prospective trials are needed to confirm whether these beneficial hemodynamic effects translate into improved clinical outcomes.

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Disclosures
Dr G. Gaemperli, Biaggi, Läsch, and Corti have received speaker’s or consultant honoraria from Abbott Vascular. Dr Schreuder is an employee and a shareholder of CD Leycom, Zoetermeer, the Netherlands. The other authors report no conflicts.

References
There is a lack of physiologic understanding of the mechanisms by which mitral valve repair may affect hemodynamic profiles, left ventricular (LV) loading conditions, and contractility. The MitraClip system is increasingly used for mitral valve repair in patients at high surgical risk and allows us to study the acute effects of reducing mitral regurgitation on the LV in a human beating heart model. This is clinically important because >50% of patients treated worldwide by percutaneous mitral valve replacement with and without chordal preservation in patients with organic mitral regurgitation. The relationship of afterload to ejection performance in chronic mitral regurgitation. Circulation. 1985;76:59–67.


CLINICAL PERSPECTIVE
Real-Time Left Ventricular Pressure-Volume Loops During Percutaneous Mitral Valve Repair With the MitraClip System

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