Real-Time Left Ventricular Pressure: Volume Loops during Percutaneous Mitral Valve Repair with the MitraClip System

Running title: Gaemperli et al.; Pressure volume loops during MitraClip

Oliver Gaemperli, MD*1; Patric Biaggi, MD*2; Remo Gugelmann1; Martin Osranek, MD1; Jan J. Schreuder, MD, PhD3; Ines Bühler1; Daniel Sürder, MD1; Thomas F. Lüscher, MD1; Christian Felix, MD4; Dominique Bettex, MD4; Jürg Grünenfelder, MD5; Roberto Corti, MD1

1Andreas Grüntzig Cardiac Catheterization Laboratories; 2Echocardiography, Cardiovascular Center, University Hospital Zurich, Switzerland; 3CD Leycom, Zoetermeer, The Netherlands; 4Dept of Anesthesiology; 5Cardiovascular Surgery, University Hospital Zurich, Switzerland

*Both authors contributed equally

Address for Correspondence:
Oliver Gaemperli, MD
Andreas Gruntzig Laboratories and Cardiac Imaging
Cardiovascular Center
University Hospital Zurich
Ramistrasse 100
8091 Zurich
Tel: +41 44 255 1052
Fax: +41 44 255 4401
E-mail: oliver.gaemperli@usz.ch

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Abstract:

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

**Methods and Results**—Pressure-volume (PV) 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%) MR. Percutaneous MVR increased end-systolic wall stress (WS_{ES}) (from (median (IQR)) 184 (140-200) to 209 (176-232) mmHg, \( P<0.001 \)) and decreased end-diastolic wall stress (WS_{ED}) (from 48 (28-58) to 34 (21-46) mmHg, \( P=0.005 \)), while end-systolic pressure-volume relationship (ESPVR) was not significantly affected. Conversely, CI increased (from 2.6 (2.2-3.0) to 3.2 (2.6-3.8) L/min/m², \( P<0.001 \)) and mean PCWP decreased (from 15 (12-20) to 12 (10-13) mmHg, \( P<0.001 \)). While changes in ΔWS_{ES} (ΔWS_{ES}) were not correlated with ΔCI, ΔWS_{ED} correlated significantly with ΔmPCWP \( (r=0.63, P<0.001) \). Total mechanical energy assessed by the pressure-volume area (PVA) remained unchanged resulting in a more favourable forward output (CI) to mechanical energy (PVA) ratio after MVR. On follow-up (153±94 days), NYHA 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 (95-191) to 127 (82-202) mL, \( P=0.036 \)).

**Conclusions**—Percutaneous MVR improves hemodynamic profiles and induces reverse LV remodeling by reducing LV preload while preserving contractility. In nonsurgical candidates with compromised LV function, MitraClip™ therapy could be considered as an alternative to surgical MVR.

**Key words:** mitral regurgitation, percutaneous mitral valve repair, hemodynamics, pressure-volume relationship
Introduction

Recently, a novel percutaneous method for mitral valve repair (MVR) has been developed. 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. Based on promising initial clinical experiences with percutaneous edge-to-edge MVR, the MitraClip™ device has been implanted in over 6000 patients worldwide. However, data on the hemodynamic consequences of percutaneous MVR are scarce, and its effect on left ventricular (LV) preload, afterload and contractility, the main determinants of LV pump performance, are yet to be investigated.

Simultaneous in vivo pressure-volume (PV) measurements with a conductance catheter (CC) placed in the left ventricle allow real-time assessment of the LV PV relationship. 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 yet, 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 purpose of this study was to investigate acute 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 mid-term clinical outcomes.
Methods

Patient Population and Study Design

We included consecutive patients undergoing percutaneous MVR using the MitraClip™ system at the University Hospital Zurich, Switzerland. Patients were selected for the procedure if they had moderate-to-severe (3+) or severe (4+) mitral regurgitation (MR), 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 to percutaneous MVR was discussed in an interdisciplinary heart valve team including an interventional cardiologist, cardiac surgeon, echocardiographer, and cardiac anesthetist. Exclusion criteria were rheumatic heart disease, endocarditis, mitral valve orifice area ≤2.0 cm², extensively 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 left and right heart catheterization and was approved by the local institutional review board.

Mitral Valve Repair Procedure

Percutaneous MVR with the MitraClip™ device (Abbott Vascular Structural Heart, Menlo Park, CA) was performed according to standard technique described elsewhere with echocardiographic (3D 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 (APS) 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 7-french flexible catheter that is placed in the left ventricle via a 0.025-inch J-tipped guide-wire. It contains a solid-state pressure sensor and 12 electrodes at regular intervals and is connected to a pressure-volume signal processor (Inca, CD Leycom). The conductance method calculates continuous LV volume tracings by measuring parallel electrical conductance between a number of electrodes situated at regular intervals along the catheter, and has been successfully validated against cine-CT and electro-conductive balloons in animals.14,15 The correct position of the conductance catheter 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 3D echocardiography (obtained under general anesthesia in the operating room immediately prior to 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 heart beats (at least 10 s for sinus rhythm, or at least 15 s in atrial fibrillation) to minimize inaccuracies from beat-to-beat variations and changes in venous return due to mechanical ventilation. In a subgroup of 31 patients, a repeat baseline recording was performed to assess reproducibility of CC measurements.

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

**Variables and Data Analysis**

CC data analysis was performed on a dedicated data acquisition and analysis software (Conduct NT, Version 3.18.1, CD Leycom) by consensus of two 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.16 The endsystolic pressure-volume relationship (ESPVR) represents the ratio of LV pressure over LV volume at the end of ventricular systole (uppermost left corner of the PV loop).17 The Starling contractile index (SCI) is calculated as the maximal rate of pressure change over time during isovolumetric contraction (+dP/dt<sub>max</sub>) normalized to end-diastolic volume (EDV). (External) stroke work (eSW) was calculated as the area within the PV loop and normalized to EDV to obtain preload-recruitable stroke work (PRSW). Pressure-volume area (PVA), a measure of total mechanical energy generated by ventricular contraction, was calculated as the sum of eSW and elastic potential energy (PE) according to the following formula:18

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

LV preload and afterload were estimated from end-diastolic and end-systolic wall stress (WS),19,20 respectively which were calculated according to the following formula for time-dependent wall stress:21
WS(t) = P(t) \cdot (1 + 3 \cdot V(t) / V_{wall})

where WS(t) is LV wall stress, P(t) LV pressure and V(t) LV volume at a given timepoint throughout the cardiac cycle. This formula assumes that wall stress is fairly uniform throughout the ventricular wall and is relatively independent of the geometry of the LV.\(^{22}\) 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 lengths of 2:1.\(^{23}\)

\[
V_{wall} = 0.8 \cdot [(IVST_d + PWT_d + EDD)^3 – EDD^3]
\]

where IVST\(_d\) is the diastolic thickness of the inter-ventricular septum, PWT\(_d\) the diastolic posterior wall thickness and EDD the end-diastolic diameter measured on M-mode echocardiography.

CO and cardiac index (CI) were calculated using the Fick method.\(^{24}\) Systemic (SVR) and pulmonary vascular resistance (PVR) were calculated as the ratio between the pressure drop along the vascular bed and the cardiac output and converted in metric units (dynes·sec·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 endpoints included death, recurrent hospitalization for congestive heart failure (CHF), mitral valve surgery, and New York Heart Association (NYHA) functional class.

LV volumes at follow-up were assessed from 2-dimensional transthoracic echocardiography using the area-length method,\(^{25}\) and systolic pulmonary pressure was
estimated from peak tricuspid regurgitant jet velocity using the Bernoulli equation.

Statistical Analysis
Statistical analysis was performed using the SPSS software package (SPSS 12.0.1 for Windows, SPSS Corp.). Quantitative data are expressed as mean±standard deviation (SD) or median with interquartile range (IQR) where appropriate, and categorical data given in proportions and percentages. Statistical comparison of quantitative data was performed using a two-tailed Wilcoxon signed rank test test for paired samples. The Friedman test was employed for repeated measurements of LV volumes. Categorical data was compared with Fisher’s exact test. Results from different measurements were correlated using Spearman’s method. Reproducibility of PV measurements was tested using 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 p value <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 etiology of mitral regurgitation was degenerative (DMR) in 16 (48%), functional (FMR) in 15 (45%), and mixed in 2 patients (6%). MR severity at baseline was 3+ in 7 (21%), and 4+ in 26 (79%) patients. Three patients had previously undergone surgical MVR with ring anuloplasty (n=2) or Alfieri stitch (n=1).
Procedural Outcome

MitraClip implantation was successful in 31/33 patients (APS 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 two patients due to excessive posterior anular calcification with poor echocardiographic image quality (n=1) or partial clip detachment (n=1). Post-interventional complication rates were low, and there was no in-hospital death. Two of the patients required vasopressor therapy over 1 – 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 (EDP) and μPAP by (median) 3, μPCWP by 5, and vPCWP by 7 mmHg, while MAP was increased by 9 mmHg. EDV remained unchanged while end-systolic volume (ESV) increased by 11 mL after MVR (p=0.006). This resulted in a reduction of ejection fraction (EF) from 55% (IQR, 45–65%) to 42% (31–56%) (P<0.001). Nonetheless, CO and CI increased significantly by 0.9 L/min and 0.5 L/min/m², respectively (Figure 1). There was no significant correlation between changes of EF (ΔEF) and ΔCI during percutaneous MVR (r=-0.33, P=0.06).

Afterload, Preload, and LV Contractility

Percutaneous MVR increased WS_{ES} by 30 mmHg (P=0.001) and lowered WS_{ED} by 8 mmHg (P=0.005) (table 2). However, no significant changes were observed for SCI and ESPVR (Figure 1). After percutaneous MVR, PRSW decreased by 3 mmHg (P=0.001).

None of the aforementioned variables of contractility (ESPVR, SCI, PRSW) correlated
significantly with changes in mPAP, and/or CI, except for PRSW which showed a poor-to-moderate, but statistically significant correlation ($r=0.395$, $P=0.025$) with CI. Changes in $\Delta WS_{ES}$ ($\Delta WS_{ES}$ did not relate to $\Delta CI$ ($r=0.004$, $P=0.98$), but there was moderate-to-good correlation between $\Delta WS_{ED}$ and $\Delta mPCWP$ ($r=0.63$, $P<0.001$) (Figure 2). Figure 3 shows individual examples for PV loops before and after percutaneous MVR.

**LV myocardial energetics**

Percutaneous MVR decreased eSW (table 2) while it increased PE (from 2,769 (1,796–4,763) to 3,921 (2,221–5,474) mmHg·mL; $P=0.001$). As a result, PVA remained unchanged. The ratio of forward CO over PVA (multiplied by heart rate to account for 1 minute of PVA) increased significantly after MitraClip™ implantation from 0.0084 (0.0065–0.0106) to 0.0091 (0.0082–0.0145 mmHg$^{-1}$; $P=0.007$) (figure 4).

**Comparison between degenerative and functional MR**

Table 3 shows a comparison of hemodynamic and CC for DMR ($n=16$) versus predominantly FMR (functional + mixed) ($n=17$) etiology. There was a similar reduction in mPAP and mPCWP in both groups, however, the decrease in EDP and $WS_{ED}$ and the increase in CI were larger in the DMR group ($P<0.05$). Notably, changes in $WS_{ES}$ were similar in both groups with no excess afterload increase in the FMR group. Interestingly, changes in ESPVR and PRSW appeared more favourable for FMR, whereas for SCI no significant differences were found between both 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, $r=0.97$; ESV, $r=0.96$; EDP, $r=0.86$; PRSW, $r=0.96$; SCI, $r=0.96$;
ESPVR, $r=0.81; \text{WS}_{ES}, r=0.80; \text{WS}_{ED}, r=0.86 (P<0.001 \text{ for all})$. Bland-Altman limits of agreement were narrow with the following RC's (given in percent of the average value): EDV, 26%; ESV, 52%, EDP, 32%; PRSW, 31%; SCI, 38%; WS$_{ES}$, 32%; WS$_{ED}$. 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 (15%) patients died and 4 (12%) were readmitted for CHF. NYHA 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 15 patients, 2+ in 4 patients, and 4+ in 3 patients. A significant stepwise reduction of EDV (from 147 (95-191) to 127 (82-202) mL, $P=0.036$) was observed over the entire period of observation (Figure 6). ESV tended to decline after discharge but the changes fell short of significance ($P=0.058$). There was no significant correlation of any of the contractility parameters at baseline (ESPVR, SCI, PRSW) with changes in EDV and ESV. Systolic pulmonary pressure on echocardiography was decreased at follow-up compared to baseline (median 32 mmHg (IQR 28 – 44 mmHg) versus 43 (35–52) mmHg; $P=0.039$). Changes in echocardiographic parameters (including volumes and EF) were similar among DMR versus FMR patients.

**Discussion**

The present study addressed the immediate effects of percutaneous MVR with the MitraClip$^\text{TM}$ on left ventricular performance (including left ventricular contractility, afterload and preload) as assessed by CC and their relationship to hemodynamic changes and clinical outcomes. Our results can be summarized as follows: (1) 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 of pulmonary pressure indicates that the beneficial effect of end-diastolic unloading outweighs the potentially negative afterload increase. (2) Despite an acute decline in EF after the MVR procedure, LV contractility measured by load-independent parameters is not significantly affected. (3) Total mechanical energy (PVA) remains unchanged and therefore myocardial oxygen consumption is not expected to increase after MVR. (4) These beneficial hemodynamic changes in combination with a preserved LV contractility appear to reverse LV remodeling by a reduction in EDV and associate to 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 left ventricular performance resulting in an acute postoperative low-output state.\textsuperscript{27-30} 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.\textsuperscript{27}

We observed a significant 21% increase in LV afterload (estimated based on \textit{W}_{SE}) 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 (\textbf{Figure 2, panel A}). 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 (\textbf{Figure 2, panel B}). 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 acute increase in stroke volume and concomitant decrease in preload. Conversely, it can be expected that decreasing the LV offloading effects of MR will acutely increase the afterload along the patients end-systolic elastance.

Contrary to the general notion, afterload tends to be high in chronic MR due to progressive ventricular enlargement particularly in the decompensated stage. Thus, an uncontrolled increase in LV afterload, also termed “afterload excess”, is an important concern after MR correction as 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 to previously mentioned studies is that we assessed cardiac loading conditions immediately (i.e. minutes) after correction of the MR whereas others used echocardiographic assessment several days after surgery allowing for early LV remodeling to take place.

Compared to patients with DMR, the reduction in LV preload (measured by EDP and WSE) 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 etiology of heart failure in these two subgroups. In DMR, the effect of MR on the LV is predominantly volume overload which can be effectively reversed by reducing or abolishing MR. However, in FMR the pathophysiology of heart failure is more complex and involves reduced contractility due to
ischemic or dilated cardiomyopathy. Hence, in this subgroup the hemodynamic response to percutaneous MVR is more difficult to predict. Nonetheless, while afterload was higher in FMR patients at baseline, there was no excess afterload increase after MVR compared to DMR (table 3). However, it should be noted that the sample size for both subgroups was small, which precludes any firm clinical conclusion.

Effects of Percutaneous MVR on Left Ventricular Contractility

We could demonstrate that despite a significant acute decline in EF, percutaneous MVR did not significantly affect LV contractility measured by ESPVR estimating the end-systolic elastance, a load-independent index of LV contractility. The SCI also did not change significantly, however its application as load-independent index of contractile state during a MVR procedure is questionable because it will already increase by decreasing protosystolic regurgitation. Also PRSW as index of contractile state is not applicable for MVR because eSW decreases due the decrease in mitral regurgitation.

Previous observations have also shown substantial disparity between ejection fraction and end-systolic indices of LV contractility in the presence of MR. Interestingly, neither load-independent parameters of LV contractility nor EF demonstrated a clinically relevant correlation to cardiac output indicating that the improvement in hemodynamic status is achieved through the reduction of regurgitant flow rather than any substantial changes in LV contractility.

Deterioration of LV contractility occurs late into the natural history of chronic mitral regurgitation and marks the transition into the chronic decompensated stage. These patients represent a challenge to available treatment options as LV changes may have reached an irreversible stage where outcomes of surgical interventions are poor. Therefore, it is crucial to avoid interventions that will lead to further deterioration of LV contractility. Interestingly,
changes in load-independent contractility parameters appeared even more favourable in our
group of patients with FMR (with even a 7% increase in SCI and ESPVR) compared to DMR (table 3). Thus, percutaneous MVR using the MitraClip™ device appears to spare LV contractility and therefore may still be considered as valuable treatment option of 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 PE. This shift represents a loss of efficiency in the transfer of energy from the PVA to external mechanical work (eSW), and has been 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 ¼ 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 which 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 favourable reverse LV remodeling. This reverse remodeling may be a result of improved hemodynamic conditions from
removing (or reducing) MR (i.e. lower LV filling pressures, improved cardiac index) in combination 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 CHF) were considerable given the substantial comorbid status of our patients. However, the limited number of subjects and the lack of a control group precludes any firm conclusion about the relationship of the observed hemodynamic changes with any potential clinical benefit. A recent non-randomized study documented superiority of percutaneous MVR compared to medical treatment in patients with predominantly functional MR 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 intra-procedural 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, blood and electrolyte loss were
limited and therefore are unlikely to play a significant confounding role.

We did not measure end-systolic elastance (i.e. the slope of the ESPVR, a load-independent index of LV contractility) as this 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 to the conscious non-sedated 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 CO and CI calculated by the Fick method than would be expected for this population. Finally, assumptions on resting oxygen consumption do not necessarily apply to the anesthetized patient and are a further limitation of the Fick principle. However, since pre- and post-procedural measurements were obtained under the same conditions, the relative changes of the latter parameters are expected to represent true changes.

Clinical implications

Despite significant morbidity and mortality, many patients with severe MR are denied surgery due to 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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Conflict of Interest Disclosures: O.G., P.B., T.F.L., and R.C. have received speaker’s or consultant honoraria from Abbott Vascular. J.J.S. is employee and shareholder of CD Leycom, Zoetermeer, The Netherlands.

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### Table 1. Baseline Characteristics (n=33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>78 ± 10</td>
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<tr>
<td>Female gender, n (%)</td>
<td>14 (42%)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>25 ± 4</td>
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<tr>
<td><strong>Clinical features, n (%)</strong></td>
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<tr>
<td>Arterial hypertension</td>
<td>21 (64%)</td>
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<tr>
<td>Hyperlipidemia</td>
<td>12 (36%)</td>
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<td>Diabetes mellitus</td>
<td>6 (18%)</td>
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<tr>
<td>Coronary artery disease</td>
<td>14 (42%)</td>
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<tr>
<td>Previous MI</td>
<td>7 (21%)</td>
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<tr>
<td>Previous PCI</td>
<td>8 (24%)</td>
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<tr>
<td>Previous CABG</td>
<td>7 (21%)</td>
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<td>Atrial fibrillation</td>
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<td>COPD</td>
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<td>Previous stroke</td>
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<td>Impaired renal function (eGFR &lt;60mL/min)</td>
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<td>Left ventricular ejection fraction, %</td>
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<td><strong>NYHA functional class, n (%)</strong></td>
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<tr>
<td>II</td>
<td>8 (24%)</td>
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<tr>
<td>III</td>
<td>20 (61%)</td>
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<tr>
<td>IV</td>
<td>5 (15%)</td>
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<td><strong>Surgical risk</strong></td>
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<td>Logistic EuroSCORE, %</td>
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<td>STS mortality score, %</td>
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<tr>
<td>STS mortality &amp; morbidity score, %</td>
<td>27 ± 12</td>
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</tbody>
</table>

Data are given as mean±SD unless otherwise stated. BMI denotes body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; EuroSCORE, European System for Cardiac Operative Risk Evaluation; STS, Society of Thoracic Surgeons.
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 – 183)</td>
<td>138 (104 – 185)</td>
<td>-9 (-21 – 5)</td>
<td>0.18</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>57 (39 – 112)</td>
<td>84 (43 – 118)</td>
<td>11 (0 – 25)</td>
<td>0.006</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>14 (11 – 17)</td>
<td>11 (8 – 14)</td>
<td>-3 (-4 – 0)</td>
<td>0.002</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>64 (56 – 72)</td>
<td>68 (60 – 77)</td>
<td>9 (-0 – 14)</td>
<td>0.02</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>28 (24 – 32)</td>
<td>25 (22 – 29)</td>
<td>-3 (-5 – 0)</td>
<td>0.001</td>
</tr>
<tr>
<td>mPCWP, mmHg</td>
<td>15 (12 – 20)</td>
<td>12 (10 – 13)</td>
<td>-5 (-8 – 2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>vPCWP, mmHg</td>
<td>22 (16 – 30)</td>
<td>14 (13 – 16)</td>
<td>-7 (-18 – 2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>mLAP, mmHg</td>
<td>15 (10 – 21)</td>
<td>11 (9 – 14)</td>
<td>-3 (-7 – 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, mmHg</td>
<td>184 (140 – 200)</td>
<td>209 (176 – 232)</td>
<td>30 (10 – 58)</td>
<td>0.001</td>
</tr>
<tr>
<td>WSED, mmHg</td>
<td>48 (28 – 58)</td>
<td>34 (21 – 46)</td>
<td>-8 (-19 – 2)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Load-independent parameters of LV contractility</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCI, mmHg/mL/s</td>
<td>4.8 (3.1 – 8.9)</td>
<td>5.8 (3.7 – 9.2)</td>
<td>0.2 (-0.5 – 1)</td>
<td>0.23</td>
</tr>
<tr>
<td>ESPVR, mmHg/mL</td>
<td>1.6 (0.7 – 2.6)</td>
<td>1.2 (0.8 – 2.1)</td>
<td>-0.1 (-0.3 – 0.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>PRSW, mmHg</td>
<td>41 (29 – 60)</td>
<td>30 (24 – 52)</td>
<td>-3 (-13 – 1)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>LV myocardial energetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eSW, mmHg*mL</td>
<td>6,357 (3,756 – 7,671)</td>
<td>4,490 (2,957 – 6,754)</td>
<td>-579 (-2,287 – 228)</td>
<td>0.004</td>
</tr>
<tr>
<td>PVA, mmHg*mL</td>
<td>9,169 (6,691 – 12,033)</td>
<td>8,634 (6,951 – 10,717)</td>
<td>-52 (-1,937 – 1,181)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Forward output and resistances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO, L/min</td>
<td>4.4 (3.5 – 5.6)</td>
<td>5.6 (4.6 – 6.5)</td>
<td>0.9 (0.3 – 1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>2.6 (2.2 – 3.0)</td>
<td>3.2 (2.6 – 3.8)</td>
<td>0.5 (0.2 – 1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SVR, dyn<em>s</em>cm⁻⁵</td>
<td>995 (796 – 1261)</td>
<td>995 (633 – 1092)</td>
<td>-95 (-209 – 12)</td>
<td>0.03</td>
</tr>
<tr>
<td>PVR, dyn<em>s</em>cm⁻⁵</td>
<td>174 (129 – 282)</td>
<td>176 (99 – 286)</td>
<td>-20 (-65 – 19)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

All values are given as median and interquartile range (IQR).

EDV denotes end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure; MAP, mean arterial pressure; mPAP, mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure; vPCWP, pulmonary capillary wedge pressure v-wave; mL.A, mean left atrial pressure; WSES, end-systolic wall stress; WSED, end-diastolic wall stress; LV, left ventricular; SCI, Starling contractile index; ESPVR, end-systolic pressure volume relationship; PRSW, preload-recruitable stroke work; eSW, external stroke work; PVA, pressure-volume area; CO, cardiac output; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.
### Table 3. Hemodynamic variables before and after MVR according to MR etiology

<table>
<thead>
<tr>
<th></th>
<th>Degenerative (n=16)</th>
<th>Non-degenerative (functional + mixed) (n=17)</th>
<th>P ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After MVR</td>
<td>Median diff</td>
</tr>
<tr>
<td>EDP, mmHg</td>
<td>14</td>
<td>9</td>
<td>-4</td>
</tr>
<tr>
<td>mPAP (mmHg)</td>
<td>28</td>
<td>26</td>
<td>-2</td>
</tr>
<tr>
<td>mPCWP (mmHg)</td>
<td>19</td>
<td>12</td>
<td>-7</td>
</tr>
<tr>
<td>WS_ES, mmHg</td>
<td>149</td>
<td>185</td>
<td>28</td>
</tr>
<tr>
<td>WS_ED, mmHg</td>
<td>40</td>
<td>25</td>
<td>-13</td>
</tr>
<tr>
<td>SCI, mmHg/mL/s</td>
<td>7.9</td>
<td>9.1</td>
<td>-0.2</td>
</tr>
<tr>
<td>ESPVR, mmHg/mL</td>
<td>2.2</td>
<td>2.0</td>
<td>-0.3</td>
</tr>
<tr>
<td>PRSW, mmHg</td>
<td>54</td>
<td>43</td>
<td>-10</td>
</tr>
<tr>
<td>eSW, mmHg/mL</td>
<td>6,470</td>
<td>4,479</td>
<td>-1,709</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.6</td>
<td>3.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* * p<0.05 for between group comparisons of baseline variables
† p<0.05 for between group comparisons of post-procedural variables
‡ p value for comparison of relative changes between groups

Abbreviations as in table 2.
Figure Legends:

**Figure 1.** (A) Percent changes in hemodynamic variables (pressures and cardiac index) and (B) in variables of left ventricular performance obtained with the conductance catheter after percutaneous MVR. Each box plot shows median (thick lines) (with the numerical value inserted in the box), quartiles (upper and lower box boundaries), and extreme values (whiskers). The small circles indicate outlier values. *P<0.05. mPAP denotes mean pulmonary artery pressure; mPCWP, mean pulmonary capillary wedge pressure, vPCWP, pulmonary capillary wedge pressure v-wave, EDP, end-diastolic pressure, CI, cardiac index. PRSW denotes preload-recruitable stroke work; SCI, Starling contractile index; ESPVR, end-systolic pressure volume relationship; WSES, end-systolic wall stress; WSED, end-diastolic wall stress.

**Figure 2.** Correlation of changes in end-systolic wall stress (ΔWSES) with changes in cardiac index (ΔCI) (A), and of end-diastolic wall stress (ΔWSED) with mean pulmonary capillary wedge pressure (ΔmPCWP) (B) during the percutaneous mitral valve repair procedure. The regression line is given in the graph.

**Figure 3.** Left ventricular (LV) response to percutaneous mitral valve repair (MVR) with the MitraClip system in 6 individuals with functional MR (FMR, left column, A-C) and degenerative MR (DMR, right column, D-F). Ejection fraction at baseline were as follows: A: 25%; B: 25%; C: 29%; D: 68%; E: 65%; F: 63%. Pressure volume (PV) loops before MVR are given in black, and after MVR in red. Note somewhat...
heterogeneous PV responses among different individuals. However, in the majority, end-systolic pressure (ESP) tends to increase after MVR. Furthermore, most of the patients show an immediate increase in end-systolic volume (except for the patient B with a markedly dilated LV at baseline). Changes in cardiac index were as follows: A: +13%; B: +39%; C: +6%; D: +41%; E: +16%; and F: -9%.

**Figure 4.** Ratio of forward cardiac output (CO) (in mL/min) divided by pressure-volume area (PVA) (in mmHg*mL) multiplied by heart rate (HR) (in min⁻¹) before and after percutaneous mitral valve repair (MVR). Each box plot shows median (thick lines), quartiles (upper and lower box boundaries), and extreme values (whiskers). The small circles indicate outlier values.

**Figure 5.** Individual changes in hemodynamic and conductance catheter parameters according to etiology of mitral regurgitation (MR) (black: degenerative MR; blue: functional MR). The box plots shows median (thick lines), quartiles (upper and lower box boundaries), and extreme values (whiskers).

**Figure 6.** End-diastolic (EDV) and end-systolic (ESV) left ventricular volumes at baseline, during MitraClip implantation (MVR) and at follow-up in 22 patients with full echocardiographic follow-up. Note that volumes at baseline and follow-up were obtained by echocardiography (echo), while volumes during the index MVR procedure were obtained from conductance catheter (CC).
Figure 1
Figure 2

A

$\Delta CI$ (mL/min/m²) vs. $\Delta WS_{ES}$ (mmHg)

$r = 0.004$

$P = 0.98$

B

$\Delta mPCWP$ (mmHg) vs. $\Delta WS_{ED}$ (mmHg)

$r = 0.63$

$P < 0.001$
Figure 3
Before MVR

After MVR

$P = 0.007$

Figure 4
Figure 5
Figure 6

Echocardiography

Conductance Catheter

Volume (mL)

Baseline Echo
CC Pre MVR
CC Post MVR
Follow-Up Echo

n=22

EDV
ESV

n=22