

# Distinct Hemodynamic Changes After Interventional Mitral Valve Edge-to-Edge Repair in Different Phenotypes of Heart Failure: An Integrated Hemodynamic Analysis

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**Background**—Percutaneous mitral valve edge-to-edge repair (pMVR) with a MitraClip is beneficial for the clinical symptoms of patients irrespective of the ejection fraction (EF). Nevertheless, the consequences on hemodynamics are poorly understood. Therefore, we used data from noninvasive pressure-volume loops to investigate the left ventricular (LV) remodeling of patients after pMVR dependent on their baseline EF.

**Methods and Results**—In 130 patients with successful pMVR, the end-diastolic pressure-volume relationship (EDPVR) and end-systolic pressure-volume relationship were estimated noninvasively from echocardiographic data. We compared EDPVR and end-systolic pressure-volume relationship at discharge and follow-up between patients with a reduced EF (<40%) and patients with a mid-ranged or preserved EF (≥40%). Reduced EF was present in 71 patients (54%). Mean follow-up duration was 277±117 days. We observed a significant reduction in degree of mitral regurgitation and an improvement in functional status at follow-up irrespective of baseline EF. In patients with a mid-ranged or preserved EF, the EDPVR and end-systolic pressure-volume relationship were shifted leftwards, suggesting an improvement in LV function. In contrast, in patients with a reduced EF, EDPVR and end-systolic pressure-volume relationship remained stable, although comparison with the baseline data indicates a rightward shift of the EDPVR. This indicates that there is no improvement in LV function after pMVR in patients with reduced EF.

**Conclusions**—The pMVR is associated with improved clinical symptoms in all patient subgroups. However, it leads to different hemodynamic responses. In patients with mid-ranged or preserved EF, we found reverse remodeling with reduced LV dilatation and increased contractility. In contrast, in patients with reduced EF, we observed no reverse remodeling and no improvement in LV function. (*J Am Heart Assoc.* 2018;7:e007963. DOI: 10.1161/JAHA.117.007963.)

**Key Words:** heart failure • hemodynamics • mitral regurgitation • percutaneous mitral valve repair • pressure-volume relationship

Mitral regurgitation (MR) is frequent in patients presenting with heart failure (HF) and is associated with increased morbidity and mortality. MR can be a trigger of HF itself (degenerative MR) or be a consequence of HF with left ventricular (LV) dilatation (functional MR [FMR]). Surgical repair or replacement of the valve is a well-established therapy.<sup>1</sup> However, benefit of conventional repair in high-risk

patients is lower because of an increased rate of perioperative complications.<sup>2,3</sup>

During the past decade, percutaneous mitral valve edge-to-edge repair (pMVR) has been established as a new therapeutic option for patients with MR. This therapy allows for an effective repair of the MR with low peri-interventional risk and a sustained improvement in symptoms.<sup>4</sup> Therefore, the

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## Clinical Perspective

### What Is New?

- Despite a good functional outcome in both groups, we observed reverse remodeling after percutaneous mitral valve edge-to-edge repair only in patients with mid-ranged or preserved ejection fraction, whereas in patients with reduced ejection fraction, an increase in stroke volume was achieved only at the cost of an increase in left ventricular dilatation.

### What Are the Clinical Implications?

- Improvement in remodeling can be documented in patients with mid-ranged or preserved ejection fraction after percutaneous mitral valve edge-to-edge repair.
- Whether this translates to improved outcome needs to be evaluated in prospective randomized controlled trials.

application of pMVR is established in many countries for both degenerative MR and FMR, in case a patient is deemed inoperable or at high risk. Noteworthy, with increasing experience and expertise, this technique is offered to a broad spectrum of patients with good procedural results.<sup>5</sup>

One fundamental hypothesis that drives use of this therapy in patients with reduced ejection fraction (EF) is that treatment of FMR induces a reverse remodeling and, thereby, improves LV function. However, reports of reverse remodeling after mitral therapies have been mixed.<sup>6,7</sup> Therefore, we sought to analyze the effect of pMVR on LV hemodynamics and reverse remodeling using a noninvasive approach.

## Methods

The present study is in compliance with the Declaration of Helsinki and was approved by the local ethics committee. Every patient gave written informed consent to the use of data records for scientific research. The data that support the findings of this study are available from the corresponding author on reasonable request.

## Study Design

We enrolled patients after MitraClip (Abbott Vascular, Redwood City, CA) procedure into a prospective observational registry. Data were obtained from before implantation, at discharge and during the follow-up visits, including transthoracic echocardiography and laboratory testing (including NT-proBNP [N-terminal pro-B-type natriuretic peptide]).

For this study, we included consecutive patients who were successfully treated with the MitraClip between January 2013 and December 2015 and who completed at least one follow-

up examination. Successful treatment was defined as implantation of at least one MitraClip and a degree of MR  $\leq 2$  after implantation.

## Echocardiographic Measurements

All examinations were performed by experienced cardiologists (D.K., E.T., E.L.), according to the recommendations of the European Association of Echocardiography for assessment of MR.<sup>8</sup> In addition, echo loops were reviewed by one of the investigators (B.S.) who was not involved in the procedure. LV end-systolic, LV end-diastolic, and global stroke volume (SV) were derived using a biplane modified Simpson's rule. The early diastolic tissue velocity was derived from tissue Doppler imaging. Pulsed-wave Doppler imaging was used to determine the early mitral inflow velocity. Forward SV was calculated from the product of the LV outflow tract diameter and the LV outflow tract velocity time integral (measured by pulsed-wave Doppler). Regurgitation volume was calculated as the difference between global and forward SV. Pre-ejection and total ejection times were derived from LV outflow tract pulsed-wave Doppler.

## Noninvasive Hemodynamic Measurements

We estimated the positions of the end-diastolic and end-systolic pressure-volume relationship (EDPVR and ESPVR, respectively) from echocardiographic data using single-beat methods.<sup>9,10</sup> Briefly, for estimation of the EDPVR, we used the method published by Klotz et al.<sup>9</sup> This method uses the equation  $EDP = \alpha \cdot EDV^\beta$  to describe the EDPVR, where EDP is the end-diastolic pressure, EDV is the end-diastolic volume, and  $\alpha$  and  $\beta$  are curve-fit parameters. This approach assumes a common underlying shape for volume-normalized EDPVRs and, therefore, the curve-fit parameters  $\alpha$  and  $\beta$  could be derived in each individual participant from a single EDV/EDP data point. EDP was derived using the equation  $EDP = (11.96 + 0.596) \cdot (\text{early mitral inflow velocity} / \text{early diastolic tissue velocity})$ .<sup>11</sup> To compare the position of the entire EDPVR, we used the calculated EDV at an EDP of 20 mm Hg (VPed20).<sup>12</sup> For this parameter, the presented method has provided a sufficient correlation with invasive measurements ( $R^2 \geq 0.70$ ).<sup>13</sup>

For estimation of the ESPVR, we used the method published by Chen et al.<sup>10</sup> This method assumes a linear ESPVR. Systolic and diastolic brachial artery cuff pressures, forward SV, EF, and an estimated normalized ventricular elastance at arterial end diastole were used to estimate the end-systolic elastance (Ees). For estimation of the end diastole, we used group-averaged values and adjusted them using the patient's EF, diastolic and systolic blood pressures, preejection time, and total ejection time. We adopted this

method to calculate the Ees in our study cohort, because it has been shown to predict the Ees sufficiently compared with invasive methods ( $r \geq 0.81^{10}$ ). We then used Ees, the echocardiography-derived end-systolic volume (ESV), and the systolic blood cuff pressure for calculation of the linear ESPVR. To compare the position of the entire ESPVR, we calculated ESV at an ESP of 120 mm Hg.

These methods were then used to compare the hemodynamic status at discharge with the hemodynamic status at follow-up.

## Statistical Analysis

To analyze the hemodynamic outcome after pMVR, we divided the patients into 2 groups: EF <40% (reduced EF) and EF  $\geq$ 40% (mid-ranged or preserved EF). Continuous variables were shown as mean $\pm$ SD if normally distributed and as median (25th–75th percentile) if nonnormally distributed. Comparison between groups was performed by either the Student *t* test (for normally distributed continuous variables) or the Wilcoxon rank test (for nonnormally distributed continuous variables). Binary variables were shown as absolute and relative frequencies and compared between groups by the  $\chi^2$  test. We displayed the EDPVR and ESPVR for each group and used paired test to compare these variables. To analyze the association between EF subgroup at baseline and hemodynamic outcome variables, we used linear-mixed models to account for repeated measurements.<sup>14</sup> Linear-mixed models included random intercepts for patients and an interaction term between EF group and time point. The models were adjusted for FMR. In addition, we performed a subgroup analysis in patients with FMR. Fixed-effects regression<sup>15</sup> was used to exploit the association of a change in VPed20 with a change in NT-proBNP as a marker of the hemodynamic equilibrium (adjusted for change in creatinine and change in MR).

## Results

### Baseline Demographics

A total of 130 patients were included. Of those patients, 71 (54%) had a preprocedural EF <40% and 59 (46%) had an EF  $\geq$ 40%. Patients with an EF  $\geq$ 40% were older and NT-proBNP was lower than in patients with an EF <40%. There were no differences in New York Heart Association (NYHA) functional class, grade of MR, EuroSCORE, or creatinine. FMR was more frequent in patients with an EF <40%. A detailed description of the baseline variables is given in Table 1. VPed20 was significantly higher in patients with EF <40%, indicating rightward-shifted EDPVRs towards larger volumes compared with patients with EF  $\geq$ 40% (Figures 1 and 2).

## Functional Outcomes

The follow-up examination was conducted after a mean of  $277 \pm 117$  days. pMVR led to a significant reduction of MR from baseline to follow-up, which was comparable in both groups (median, 1.0 [25th–75th percentile, 1.0–2.0] for EF <40% versus median, 1.0 [25th–75th percentile, 1.0–2.0] for EF  $\geq$ 40%;  $P=0.16$ ). Most patients in both groups had MR  $\leq$ 2 (88.0% versus 90.0%;  $P=0.79$ ). Irrespective of baseline EF, we saw a significant reduction in NYHA functional class (median, 3.0 [25th–75th percentile, 3.0–3.0] at baseline versus median, 2.0 [25th–75th percentile, 2.0–3.0] at follow-up;  $P<0.01$  for both groups). The mitral gradient after pMVR was higher in the group with the mid-ranged or preserved EF, although the difference is not clinically relevant (median, 3.0 [25th–75th percentile, 2.0–4.0] mm Hg versus median, 4.0 [25th–75th percentile, 3.0–6.0] mm Hg;  $P<0.01$ ).

### Hemodynamic Outcomes in Patients With Mid-Ranged or Preserved EF (EF $\geq$ 40%)

From discharge to follow-up, pMVR induced a leftward shift of the EDPVR in patients with an EF  $\geq$ 40%, as represented by the significant reduction in VPed20 (mean $\pm$ SD,  $128.1 \pm 44.7$  versus  $115.5 \pm 32.7$  mL;  $P<0.01$ ; Figure 1). Although there was no change in EDP or the stiffness-coefficient  $\beta$ , EDV significantly decreased after pMVR. Taking the baseline measurements into account further supports these findings. Herein, we saw a decrease in VPed20 from baseline to follow-up (mean $\pm$ SD,  $129.5 \pm 40.8$  versus  $115.5 \pm 32.7$ ;  $P<0.01$ ).

For the ESPVR, we observed a leftward shift, because calculated ESV at an ESP of 120 mm Hg was significantly reduced from discharge to follow-up (mean $\pm$ SD,  $75.5 \pm 37.1$  versus  $65.9 \pm 34.8$  mL;  $P=0.03$ ) with a stable Ees. The baseline measurements not only support these findings by showing a decrease in calculated ESV at an ESP of 120 mm Hg (mean $\pm$ SD,  $78.4 \pm 36.5$  versus  $65.2 \pm 34.6$  mL;  $P<0.01$ ), but indicate an increase in Ees (mean $\pm$ SD,  $1.5 \pm 0.6$  versus  $2.0 \pm 1.0$ ;  $P<0.01$ ). We observed an increase in global EF and a stable global SV while, at the same time, we observed a stable forward EF and a slight decrease in forward SV from discharge to follow-up (Table 2). Figure 2 illustrates the hemodynamic changes in patients with an EF  $\geq$ 40%. Table 2 gives a more detailed overview about hemodynamic outcome variables. In addition, adjustment of the linear-mixed models for FMR revealed no significant impact of this variable on the hemodynamic outcome in these patients. Detailed hemodynamic outcome data of the subgroup of patients with FMR are displayed in Table 3.

**Table 1.** Baseline Data of the Study Population

Characteristics	All Patients (N=130)	EF <40% (n=71)	EF ≥40% (n=59)	P Value
Age, y	75.1±8.6	73.0±9.2	77.6±7.2	<0.01
Sex (male)	73 (56.2)	44 (62.0)	29 (49.2)	0.20
EuroSCORE, %	22.4±14.1	24.5±16.1	19.7±10.6	0.06
Diabetes mellitus	31 (24.0)	19 (26.8)	12 (20.7)	0.55
COPD	19 (14.7)	10 (14.1)	9 (15.5)	1.00
Hypertension	98 (75.4)	48 (67.6)	50 (84.7)	0.04
Dyslipidemia	36 (28.8)	12 (17.4)	24 (42.9)	<0.01
Atrial fibrillation	85 (65.9)	43 (61.4)	42 (71.2)	0.33
CAD	76 (58.5)	45 (63.4)	31 (52.5)	0.28
Creatinine, mg/dL	1.5±0.8	1.5±0.5	1.6±1.0	0.88
NYHA functional class				
I	1 (0.8)	0 (0.0)	1 (1.8)	0.44
II	10 (7.9)	5 (7.0)	5 (8.9)	0.75
III	89 (70.1)	50 (70.4)	39 (69.6)	1.00
IV	27 (21.3)	16 (22.5)	11 (19.6)	0.86
NT-proBNP, ng/L	4816 (2417–7840)	5301 (3136–9164)	3819 (2016–4920)	0.01
Grade of MR	4.0 (3.0–4.0)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	0.59
FMR	95 (73.1)	63 (88.7)	32 (54.2)	<0.01
EF, %	39.4±13.5	29.1±6.2	51.8±8.5	<0.01
AR (grade)	0 (0–1.0)	1.0 (0–1.0)	0 (0–1.0)	0.11
AS (grade)	0 (0–0)	0 (0–0)	0 (0–1.0)	0.33
TR (grade)	2.0 (1.0–3.0)	2.0 (1.0–2.8)	2.0 (1.0–3.0)	0.12
ACE-I	74 (57.8)	42 (60.0)	32 (55.2)	0.71
ARB	17 (13.5)	12 (17.1)	5 (8.9)	0.28
β Blockers	107 (83.6)	57 (81.4)	50 (86.2)	0.63
MRA	47 (37.6)	36 (52.2)	11 (19.6)	<0.01
Diuretics	116 (91.3)	65 (94.2)	51 (87.9)	0.35

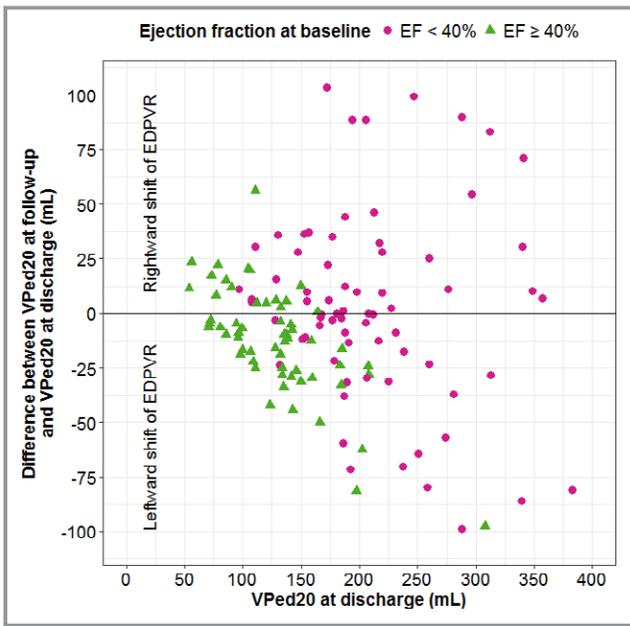
Values are presented as mean±SD if normally distributed, median (25th–75th percentile) if nonnormally distributed, or absolute (relative) frequencies. ACE-I indicates angiotensin-converting enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin receptor blocker; AS, aortic stenosis; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; FMR, functional MR; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and TR, tricuspid regurgitation.

### Hemodynamic Outcomes in Patients With Reduced EF (EF <40%)

The pMVR induced no relevant shift of the EDPVR from discharge to follow-up in patients with an EF <40%, as indexed by a stable VPed20 (mean±SD, 211.3±65.4 versus 214.1±73.8 mL;  $P=0.60$ ; Figure 1). EDV, EDP, and the stiffness-coefficient  $\beta$  remained stable until follow-up. However, the baseline measurements indicate an overall rightward shift of the EDPVR as for an increase in VPed20 (mean±SD, 199.4±57.6 versus 214.1±73.8 mL;  $P<0.01$ ) and EDV (mean±SD, 200.0±58.9 versus 222.0±76.5 mL;  $P<0.01$ ) from baseline to follow-up.

There were no significant changes in the ESPVR: calculated ESV at an ESP of 120 mm Hg (mean±SD, 181.8±73.3 versus 182.1±82.6 mL;  $P=0.97$ ) and Ees (mean±SD, 1.1±0.4 versus 1.1±0.5;  $P=0.72$ ) did not differ between discharge and follow-up examinations. Taking the baseline measurements into account did not change these results.

We did not observe a change in forward EF (mean±SD, 27.9±9.2 versus 27.5±10.7 mL;  $P=0.66$ ) or global EF (mean±SD, 28.4±7.9% versus 29.0±10.1%;  $P=0.49$ ). However, the baseline data indicate a significant increase in forward SV (mean±SD, 45.0±14.8 versus 53.7±12.9 mL;  $P<0.01$ ) and forward EF (mean±SD, 23.8±7.8% versus 27.0±10.6%;  $P<0.01$ ). Figure 2 illustrates the hemodynamic



**Figure 1.** Visualization of the hemodynamic outcome after percutaneous mitral valve edge-to-edge repair in patients with an ejection fraction (EF)  $\geq 40\%$  and patients with an EF  $< 40\%$ . Patients are compared on the basis of their calculated end-diastolic volume at an end-diastolic pressure of 20 mm Hg (VPed20) as a marker of the end-diastolic pressure-volume relationship (EDPVR). The y axis displays the change in VPed20 from discharge to follow-up, and the x axis displays the value of the VPed20 at discharge.

changes in patients with an EF  $< 40\%$ . Table 2 gives a more detailed overview about hemodynamic outcome variables. Furthermore, adjustment of the linear-mixed models for FMR revealed no significant impact of this variable on the hemodynamic outcome in these patients. Detailed hemodynamic outcome data of the subgroup of patients with FMR are displayed in Table 3.

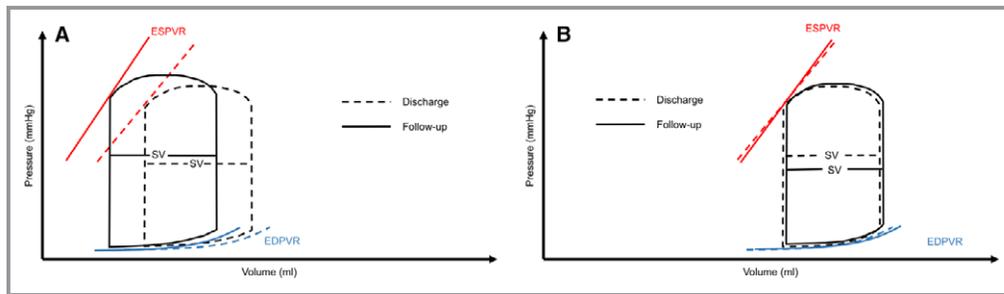
### Association of VPed20 and NT-proBNP

Paired NT-proBNP values were available in 69% of the patients. Using a fixed-effects regression analysis, we observed an association of VPed20 with NT-proBNP (Figure 3). The regression coefficient for change in VPed20 is 674.68 ( $P < 0.01$ ; ie, each 10-mL increase in VPed20 causes NT-proBNP to increase by 674.68 ng/L). The reverse is also true. Adjusting for a change in creatinine or for discharge MR did not change the association.

### Discussion

The present study is the first to address the hemodynamic effects of pMVR on LV hemodynamics in different phenotypes of HF during an extended follow-up. The main finding is that there are distinct hemodynamic responses after pMVR based on the baseline EF, despite similar improvements in NYHA functional class. In patients with mid-ranged or preserved EF, we observed reverse remodeling with reduced LV volumes and an increase in contractility. On the contrary, in patients with reduced EF, we saw no reverse remodeling.

The pMVR increases LV afterload, because the lower regurgitation volume shifts LV flow from the low-pressure left atrium to the high-pressure aorta. This short-term effect has been shown before by invasive pressure-volume-loop measurements during pMVR.<sup>16</sup> In this study, we investigated the effect of pMVR on LV hemodynamics during a mean follow-up of 277 days. As expected and shown by others, we demonstrated a significant reduction of MR grade and, thereby, a reduction of regurgitation volume in all patients. In addition, all patients improved in terms of NYHA functional class to a similar degree. However, we saw distinct hemodynamic responses to these new loading conditions during the follow-up, depending on baseline EF.



**Figure 2.** Schematic visualization of the average hemodynamic outcome after percutaneous mitral valve edge-to-edge repair in regard to baseline ejection fraction (EF). In patients with an EF  $\geq 40\%$ , the end-diastolic pressure-volume relationship (EDPVR) and end-systolic pressure-volume relationship (ESPVR) shift leftwards (A). In patients with an EF  $< 40\%$ , the EDPVR and ESPVR both remain stable (B). SV indicates stroke volume.

**Table 2.** Hemodynamic Outcome Data of the Study Population

Variables	EF <40% (n=71)			EF ≥40% (n=59)		
	Discharge	Follow-Up	P Value	Discharge	Follow-Up	P Value
VPed20, mL	211±65.4	214.1±73.8	0.60	128.1±44.7	115.5±32.7	<0.01
β	6.2 (5.1–7.5)	6.3 (5.1–7.2)	0.44	6.8 (6.2–7.7)	6.4 (6.0–8.0)	0.38
E	1.25±0.26	1.3±0.31	0.28	1.42±0.29	1.5±0.39	0.19
e'	0.06±0.02	0.06±0.02	0.28	0.08±0.03	0.08±0.03	0.82
EDP, mm Hg	25.6±5.2	26.7±6.1	0.09	24.0±3.6	25.0±5.7	0.23
EDV, mL	217.2±66.8	222.0±76.5	0.35	132.3±45.5	121.0±35.2	<0.01
VPes120, mL	181.8±73.3	182.1±82.6	0.97	75.5±37.1	65.9±34.8	0.03
V0, mL	53.8±56.6	34.7±80.8	0.07	−7.1±31.0	−12.2±29.8	0.12
Ees	1.1±0.4	1.1±0.5	0.72	1.8±0.7	2.0±1.0	0.11
ESP, mm Hg	102.0±14.0	105.7±17.6	0.06	110.6±16.0	119.8±18.3	<0.01
ESV, mL	158.8±60.3	162.4±70.6	0.40	70.6±31.0	62.4±26.6	<0.01
Forward SV, mL	55.1±14.2	54.0±13.2	0.60	61.7±19.8	55.8±14.4	<0.01
Forward EF, %	27.9±9.2	27.5±10.7	0.66	47.7±11.0	47.6±10.7	0.93
Global SV, mL	58.2±14.8	59.6±16.2	0.47	62.0±21.3	58.6±14.9	0.07
Global EF, %	28.4±7.9	29.0±10.1	0.49	47.4±9.2	49.7±9.6	0.03
Systolic blood pressure, mm Hg	112.9±15.7	116.7±19.6	0.07	122.6±17.5	132.9±20.3	<0.01
Diastolic blood pressure, mm Hg	67.5±10.0	67.4±10.1	0.93	69.3±12.5	72.6±11.9	0.05
Heart rate, bpm	73.0±11.7	70.7±11.2	0.08	74.8±15.4	72.3±14.0	0.20

β indicates stiffness coefficient; bpm, beats per minute; E, early mitral inflow velocity; e', early diastolic tissue velocity; EDP, end-diastolic pressure; EDV, end-diastolic volume; Ees, end-systolic elastance; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; SV, stroke volume; V0, calculated ESV at an ESP of 0 mm Hg; VPed20, calculated EDV at an EDP of 20 mm Hg; and VPes120, calculated ESV at an ESP of 120 mm Hg.

### Patients With Mid-Ranged or Preserved EF (EF ≥40%)

In patients with EF ≥40%, both the EDPVR and the ESPVR were significantly shifted leftwards during follow-up. The former indicates that the LV EDV at a given end-diastolic pressure is lower after pMVR. This decrease in LV capacitance and reverse remodeling represents a change in LV structure towards normal, but, on average, hearts were still larger than normal on the basis of a comparison of VPed20 values from a population-based study.<sup>17</sup> Correspondingly, the ESPVR was shifted leftward after pMVR, indicating increased LV contractility.<sup>12</sup> This was accompanied by increased global EF, because the EDV decreased, with the global SV being relatively stable. The forward SV decreased to a clinically not relevant extent; this, however, did not lead to a significant change in forward EF.

Our analysis thus shows that the positive effect of pMVR in patients with EF ≥40% is not only reflected by improved EF. More important, the positive effect relates to reverse remodeling with less LV dilatation and increased LV contractility. This is further encouraged by the positive

association of a change in EDPVR with NT-proBNP (Figure 3).

Our findings in patients with EF ≥40% fit well with conclusion of prior studies on pMVR. The EVERST II (Endovascular Valve Edge-to-Edge Repair Study), a randomized controlled trial comparing pMVR with a surgical approach in symptomatic MR, observed 327 patients after pMVR, with a mean baseline EF of 47.5%. Besides a sustained reduction of MR and an improvement in clinical symptoms, the authors report a reduction in EDV and ESV, as well.<sup>18</sup> In another retrospective study, Rudolph et al report on echocardiographic follow-up data after pMVR in 63 patients with severe MR and mean EF 43% not amendable for surgery. Herein, a decrease in EDV and ESV was as well shown.<sup>19</sup>

However, displaying volume-based parameter only, as in the studies previously mentioned, does not sufficiently describe LV hemodynamics. This approach neglects load-dependent changes and may lead to deceptive results. The present study is the first to report on hemodynamic changes after pMVR over an extended follow-up in an integrated and load-independent manner using pressure-volume analysis. Therefore, comparison of our results to those of others may be limited.

**Table 3.** Hemodynamic Outcome Data of the Subgroup of Patients With FMR

Variable	Patients With FMR With EF <40% (n=63)			Patients With FMR With EF ≥40% (n=32)		
	Discharge	Follow-Up	P Value	Discharge	Follow-Up	P Value
VPed20, mL	211.8±66.9	215.7±76.7	0.47	141.3±50.9	123.9±34.2	<0.01
β	6.2 (5.1–7.6)	6.3 (5.1–7.6)	0.42	6.4 (6.1–7.2)	6.7 (6.1–8.1)	0.40
E	1.25±0.26	1.3±0.32	0.33	1.38±0.32	1.5±0.4	0.17
e'	0.06±0.02	0.05±0.01	0.19	0.08±0.03	0.07±0.03	0.67
EDP, mm Hg	25.7±5.2	27.0±6.2	0.07	23.4±3.9	25.5±6.6	0.12
EDV, mL	217.6±68.2	223.8±79.5	0.25	144.0±50.3	128.2±35.2	<0.01
VPes120, mL	181.4±73.4	182.1±84.5	0.92	86.6±41.4	73.8±35.5	0.02
VO, mL	51.4±58.5	32.3±82.7	0.10	−6.1±32.6	−7.1±26.4	0.80
Ees	1.1±0.4	1.0±0.5	0.95	1.6±0.8	1.8±0.8	0.21
ESP, mm Hg	100.8±13.7	105.0±17.4	0.04	109.8±13.6	119.7±19.5	<0.01
ESV, mL	158.7±61.6	163.6±73.0	0.29	78.2±32.2	68.3±25.0	<0.01
Forward SV, mL	55.0±14.7	54.1±13.5	0.67	64.4±21.1	56.3±15.4	0.01
Forward EF, %	28.2±9.5	27.7±10.8	0.61	46.0±11.4	44.9±9.4	0.56
Global SV, mL	58.6±15.2	60.3±16.9	0.44	65.8±23.6	59.9±15.6	0.04
Global EF, %	28.6±8.1	29.1±10.4	0.58	46.1±9.1	47.5±8.0	0.34
Systolic blood pressure, mm Hg	111.7±15.5	116.1±19.4	0.04	122.0±15.2	133.0±21.7	<0.01
Diastolic blood pressure, mm Hg	66.3±9.6	67.6±10.1	0.35	68.5±11.9	73.7±12.5	0.04
Heart rate, bpm	73.5±12.0	71.0±11.3	0.07	73.6±16.4	72.0±14.0	0.59

β indicates stiffness coefficient; bpm, beats per minute; E, early mitral inflow velocity; e', early diastolic tissue velocity; EDP, end-diastolic pressure; EDV, end-diastolic volume; Ees, end-systolic elastance; EF, ejection fraction; ESP, end-systolic pressure; ESV, end-systolic volume; FMR, functional mitral regurgitation; SV, stroke volume; VO, calculated ESV at an ESP of 0 mm Hg; VPed20, calculated EDV at an EDP of 20 mm Hg; and VPes120, calculated ESV at an ESP of 120 mm Hg.

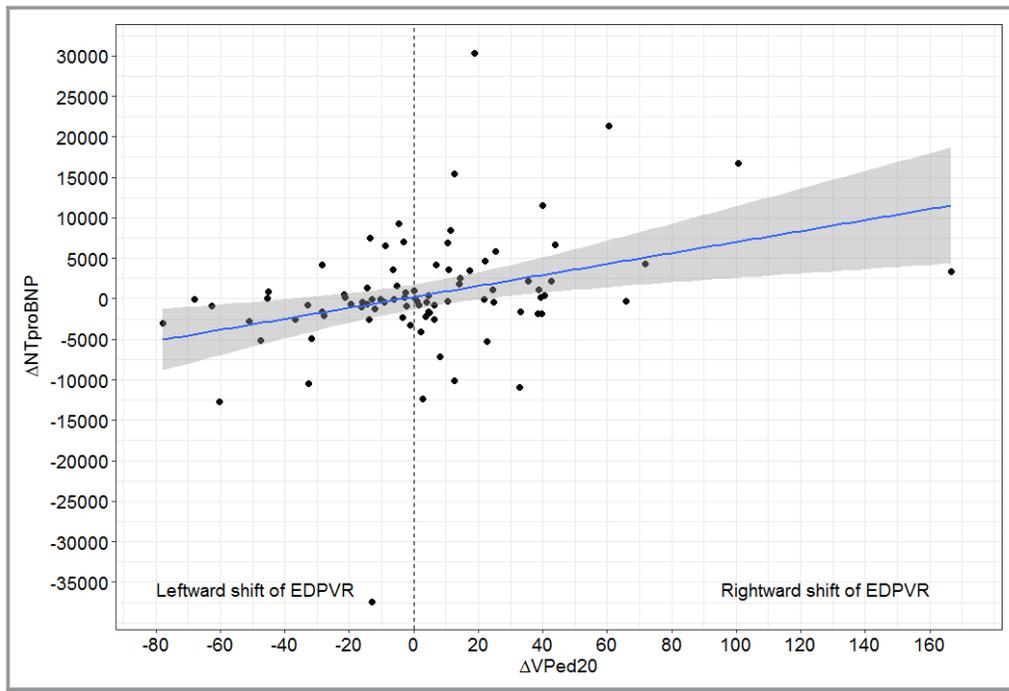
### Patients With Reduced EF (EF <40%)

Most interestingly, we observed different hemodynamic changes after pMVR in patients with reduced EF during the follow-up. In this subset of patients, we saw no shift of the EDPVR nor the ESPVR from discharge to follow-up. In contrast to the previously mentioned findings, this indicates that pMVR apparently does not stop nor reverse the preexisting LV dilatation in patients with reduced EF compared with patients with preserved EF. More so, the baseline data even indicate an increase in LV dilatation after pMVR by a significant increase in EDV and EDPVR (although it has to be taken into account that the noninvasive measurement of the EDPVR is not validated in the context of a relevant MR). Interestingly, in patients with an EF <40% at baseline, both forward SV and forward EF increased after pMVR, whereas global SV and global EF remained stable. This indicates that the redirection of the regurgitation volume on the one hand leads to an augmentation of the forward SV, which is most likely part of the improved function status after pMVR in this group. On the other hand, the increase in afterload (as an adverse effect of redirecting blood from the low-pressure left atrium into the high-pressure aorta) seems not to be met by a sufficient

contractile reserve in this group, which might explain the tendency towards an increase in LV dilatation. However, it is unknown whether there would have been more pronounced LV dilatation in these patients without prior pMVR. In this context, future studies comparing pMVR to optimal medical therapy will be of great interest.

There are only few hemodynamic data available showing the effects of pMVR in patients with a reduced EF. Berardini et al<sup>6</sup> report on the echocardiographic outcome in 68 patients with pMVR for severe MR and a mean EF of 30%. In their study population, there were no changes in EF, LV ESV, or LV EDV.<sup>6</sup> These findings are in line with our observations. In another retrospective study of 40 patients with a mean EF of 33% who underwent pMVR for severe MR, the authors report an increase in global EF and a reduction in the LV end-systolic diameter after 12 months,<sup>7</sup> which contrasts with our observations. A potential explanation for this discrepancy may be survivor bias. Because of the smaller patient number and the longer follow-up in this study, positive outliers may have had a stronger impact on the outcome. In addition, LV diameter correlates to LV volumes only to a limited extent.

Our results contrast those of a larger randomized trial of surgical treatment of MR in patients with an EF of ≈40%.<sup>20</sup>



**Figure 3.** A change in the calculated end-diastolic volume at an end-diastolic pressure of 20 mm Hg (VPed20) is associated with a change in NT-proBNP (N-terminal pro-B-type natriuretic peptide) in our analysis. The regression coefficient for change in VPed20 is 674.68 ( $P < 0.01$ ;  $R^2 = 0.33$ ; ie, each 10-mL increase in VPed20 causes NT-proBNP to increase by 674.68 ng/L). The reverse is also true. EDPVR indicates end-diastolic pressure-volume relationship.

This study observed a positive effect of surgical treatment of severe MR (either with valve repair or valve replacement) on reverse remodeling (indexed by ESV).<sup>20</sup> Herein, the different findings may be explained by the vast discrepancy in the study population (eg, higher frailty and significantly lower EF in our cohort) and the different method (annuloplasty/chordae-sparing repair versus edge-to-edge repair).

### Patients With FMR

Our analysis indicates that FMR does not negatively influence the hemodynamic outcome after pMVR, irrespective of baseline EF, because we observed no relevant impact on EDPVR or ESPVR parameters in the linear mixed models and comparable hemodynamic changes in the subanalysis of FMR-only patients. However, this seems to counteract the fundamental hypothesis that treatment of FMR leads to a reverse remodeling, because we as well saw no positive hemodynamic impact in all patients with FMR. Because no prior study reported in-depth hemodynamic follow-up data on this topic, comparison to other findings is limited. In this regard, the ongoing COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial, a prospective randomized trial that compares pMVR with

optimal medical therapy in patients with HF with FMR, will be of great importance.

### Similar Clinical Benefit Despite Distinct Hemodynamic Changes

For the procedural and functional outcomes at follow-up, we saw no significant differences between the 2 groups. The reduction in MR was sustained, and there was a significant decrease in NYHA functional class in both groups. These findings are in line with many other studies that reported good procedural and functional outcomes after pMVR for severe MR, irrespective of baseline EF.<sup>5,21</sup> Therefore, we observed a similar clinical effect, despite distinct hemodynamic changes in patients with EF  $\geq 40\%$  versus patients with EF  $< 40\%$ . We speculate that patients with EF  $\geq 40\%$  benefit from reverse remodeling, whereas patients with EF  $< 40\%$  benefit from increased forward SV and, thereby, from an increase in cardiac output. A longer follow-up may uncover the long-term effects of progressive LV dilation after pMVR in patients with EF  $< 40\%$ , as indicated by our baseline data. In addition, it must be considered that improvements in symptoms and functional class are subject to placebo effects in an unblinded treatment-only study.

## Study Limitations

There are some limitations that need to be addressed. First, there is a survivor bias because only patients with successful pMVR and a complete follow-up examination were included into the analysis. Although we believe that the high patient number in both groups does limit the impact of outliers, a certain influence may not be neglected. Second, our data predict neither the natural course of the disease nor the effect of optimal medical therapy alone, because there was no control group without pMVR included. In addition, we cannot account for a change in HF medication. However, because at our institution, patients with MitraClip are only implanted after verifying that guideline-based HF medication is prescribed, we believe that this should have limited influence. Third, this is a retrospective analysis and, therefore, our results need to be validated in a prospective randomized controlled trial. Most important, the used methods to estimate the LV volumes, EDPVR, and ESPVR rely mainly on approximation formula. Although these methods have been validated invasively<sup>9,10,13</sup> and although we only included successful pMVR cases with a discharge MR  $\leq 2$ , the presence of even a mild MR potentially introduces a source of error. However, this source of error applies to all patients and, therefore, to both groups in the same extent. In addition, this approach is the only applicable way to derive hemodynamic data in these patients over a follow-up, because repetitive invasive measurements are not feasible. Therefore, we advocate to see our results as hypothesis generating and to apply this hypothesis to upcoming randomized trials.

## Conclusion

We demonstrate a sustained reduction in MR and improved functional class after pMVR irrespective of baseline EF. However, the long-term effects on LV hemodynamics differed between EF subgroups. In patients with mid-ranged or preserved EF ( $\geq 40\%$ ), we found reverse remodeling with reduced LV dilatation and increased contractility. In contrast, our data do not show such changes in patients with reduced EF ( $< 40\%$ ) but actually indicate an increase in LV dilatation, despite increased forward SV. Thus, clinical improvement after pMVR may derive from different effects in these subgroups. The implications of these findings for clinical outcome measures, such as mortality and HF hospitalizations, remain to be studied in prospective trials.

## Disclosures

Lubos and Schäfer have received speaker's honoraria from Abbott Vascular. Lubos received research funding and

traveling compensation. Schäfer is a faculty member at Crossroads Abbott Vascular in Brussels, Belgium. Besides that, he received research funding and traveling compensation. The remaining authors have no disclosures to report.

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