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ORIGINAL ARTICLE

Percutaneous edge-to-edge mitral valve repair for mitral regurgitation improves heart failure symptoms in heart failure with preserved ejection fraction patients

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Abstract

Aims Therapeutic options for patients with heart failure with preserved ejection fraction (HFpEF) are sparse. Mitral regurgitation (MR) is a common feature of HFpEF and worsens heart failure symptoms and prognosis. Our study examines the outcome of patients with preserved left ventricular ejection fraction (LVEF) and elevated left atrial (LAP) or left ventricular filling pressures (LVEDP), indicative of HFpEF, after undergoing percutaneous edge-to-edge mitral valve repair (pMVR) for moderate–severe MR.

Methods and results Two hundred eleven patients with preserved LVEF (>50%), who underwent pMVR, were dichotomized by LAP (< / ≥15 mmHg) and LVEDP (< / ≥16 mmHg). Forty-nine per cent of patients showed elevated LAP, and LVEDP was elevated in 55%, both indicating HFpEF. Patients with elevated filling pressures featured typical clinical characteristics of HFpEF, higher N-terminal pro-brain natriuretic peptide levels (5544.9 pg/mL in high LAP group vs. 3071.7 pg/mL in normal LAP group, $P = 0.06$; 5061.0 pg/mL in high LVEDP group vs. 3230.3 pg/mL in normal LVEDP group, $P = 0.08$), and higher prevalence of pulmonary hypertension (mean pulmonary artery pressure 36.4 mmHg in high LAP group vs. 26.3 mmHg in normal LAP group, $P < 0.001$; 35.2 mmHg in high LVEDP group vs. 29.7 mmHg in normal LVEDP group, $P = 0.004$) and atrial fibrillation (78.8% in normal LAP group vs. 61.0% in high LAP group, $P = 0.04$; 75.3% in high LVEDP group vs. 67.5% in normal LVEDP group, $P = 0.25$). Pre-treatment MR grade and New York Heart Association (NYHA) class were similar in both normal filling pressure and HFpEF groups. pMVR in HFpEF patients achieved effective heart failure symptom relief comparable with patients with normal filling pressures: significant decrease of MR grade and NYHA class, as well as significant reduction of heart failure hospitalizations 12 months after compared with 12 months before MitraClip.

Conclusion Percutaneous edge-to-edge mitral valve repair for moderate–severe MR is an effective treatment option for symptom relief in HFpEF patients.

Keywords Heart failure with preserved ejection fraction; Mitral regurgitation; MitraClip

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Introduction

Mitral valve regurgitation (MR) is a frequent feature of patients presenting with heart failure (HF) and can be detected in up to 75% of HF patients of various stages.[1] MR can be specified as 'primary', when the mechanism of MR is originated in the valve apparatus itself (i.e. mitral leaflets, chordae tendineae, papillary muscles, or annulus). 'Secondary' or 'functional' MR (FMR) occurs without apparent valvular disease and is often due to left ventricular (LV) dysfunction with mitral annulus dilatation and/or restricted leaflet motion.[1] Percutaneous edge-to-edge mitral valve

repair (pMVR) has been well established in treatment of primary and secondary MR with suitable anatomical characteristics and high surgical risk.[2] pMVR for FMR has been shown to reduce hospitalization rates for HF as well as all-cause mortality compared with optimal medical therapy.[3] While ventricular mechanisms of FMR have been well described, the occurrence of FMR in atrial fibrillation (AF) and/or heart failure with preserved ejection fraction (HFpEF) has remained largely unspoken. Both AF and HFpEF are closely related, and their symptoms overlap with symptoms of MR. Annular dilatation and impaired annular dynamics as well as insufficient leaflet growth or atriogenic leaflet tethering through increasing annulo-papillary distance are seen as mechanical culprits of atrial FMR.[4,5] The presence of MR in HFpEF patients can further impair functional capacity and is associated with an increased risk for adverse events.[6,7] HFpEF itself accounts for more than 50% of HF cases and should be suspected in patients presenting with symptoms of HF with preserved left ventricular ejection fraction (LVEF) and at least one typical risk factor (e.g. age, arterial hypertension, or diabetes mellitus). Making a firm diagnosis of HFpEF, however, can be challenging. Apart from scoring systems such as the H_2FPEF score helping to identify HFpEF candidates,[8] elevated left atrial (LAP) or left ventricular end-diastolic pressures (LVEDP) determine the diagnosis of HFpEF.[9]

In this study, we analysed the effect of elevated LAP and LVEDP on the outcome of patients with preserved ejection fraction (EF) after pMVR.

Methods

For this study, we assessed 618 consecutive patients receiving pMVR at our centre between January 2010 and December 2018. All patients underwent diagnostic work-up prior to the pMVR as previously described.[10] Flow limiting coronary artery disease (>50%) was ruled out by coronary angiography. Patients were on optimal medical HF therapy according to present guidelines. Two hundred eleven patients (34%) with preserved LVEF (>50%) were selected consecutively. One hundred ninety-five (92%) of these patients completed a full 12 month follow-up. LAP data were available in 163 patients (77%). In cases where LAP was unknown, pulmonary capillary wedge pressure (PCWP) was considered a surrogate. LVEDP data were available in 177 patients (84%).

The study was ethically approved by the ethics committee of the University of Ulm and complied with the principles outlined in the Declaration of Helsinki (*Br Med J* 1964; ii: 177). Nearly all patients included in the present study were symptomatic in terms of HF [New York Heart Association (NYHA) functional class ≥ II] despite guideline-directed medical therapy. Device success was defined as clip implantation with a reduction of the mitral regurgitation of more than two degrees.[11]

Patients were dichotomized by LAP and LVEDP levels. Cut-offs of ≥15 and ≥16 mmHg, respectively, were chosen according to suggestions for the diagnosis of HFpEF in current literature.[9] After dichotomization, the occurrence of all-cause and cardiovascular mortality, rehospitalization due to HF, and major adverse cardiac and cerebrovascular events (MACCE, composite endpoint of rehospitalization due to HF, neurological events or bleeding, further reintervention on the mitral valve, need for LV assist device, and mortality) were analysed.

Severity of MR was classified in four degrees according to the EVEREST criteria for MR quantification.[12] Most included patients had severe MR (i.e. grade III/IV) except for 19 patients with dynamic high-grade MR. Echocardiographic characteristics at baseline were available for all study patients. The LV end-diastolic diameters (LVEDd) were measured by transthoracic echocardiography in the parasternal long-axis view. LVEF was measured using the biplane Simpson's method. MR severity was assessed by 2D and 3D transesophageal echocardiography after final device placement and removal of guide catheter. MR was semi-quantitatively assessed by visual estimation of MR jet area and by (biplane) determination of the vena contracta of the major MR jet. In addition to MR severity, mitral valve gradients and area by pressure half-time method and in 3D technique were assessed before MitraClip deployment and after deployment and removal of the guide catheter.

The H_2FPEF score was calculated as described previously.[8]

NYHA class and echocardiographic and clinical outcome was evaluated after 12 months.

Statistical analysis was performed using Statistica 7 (StatSoft Inc, Tulsa, USA) and SPSS software (IBM Corp., Armonk, USA). Analyses were performed in the following subgroups: patients with normal LAP (<15 mmHg, n = 59) vs. elevated LAP (≥15 mmHg, n = 104) and patients with normal LVEDP (<16 mmHg, n = 80) vs. elevated LVEDP (≥16 mmHg, n = 97).

Categorical variables are expressed as counts and percentages and were compared by χ^2 test or Wilcoxon test for paired variables. Continuous parameters are presented as the mean ± standard deviation and were compared with t-test, two-way ANOVA, or Mann–Whitney test for unpaired comparisons. All-cause and cardiovascular mortality, MACCE, and rehospitalization were examined using log-rank analysis. If the cause of death was unknown, the cause was considered cardiovascular.

To identify predictors of rehospitalization due to HF, univariate analysis was performed for the two LVEDP groups for all potential influential variables (significant $P < 0.05$, and probable $P < 0.10$). In multivariate Cox regression analysis, a backward stepwise algorithm was applied to all potential influential parameters ($P < 0.10$) from univariate

Cox regression analysis. Variables that were included in the multivariate model were LVEDP ≥ 16 mmHg and ≥25 mmHg, respectively, Troponin T, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Receiver operating characteristic (ROC) analysis was carried out for the diagnostic ability of LVEDP to predict rehospitalization. Performance was tested using Youden's *J* statistic. Differences were considered statistically significant when $P < 0.05$.

Results

Baseline characteristics

Of the 618 patients receiving pMVR, 211 patients (34%) with preserved LVEF (>50%) were identified. One hundred four of these patients (49%) showed elevated LAP levels (≥15 mmHg); 59 patients (28%) had normal LAP (<15 mmHg). Between both groups, patients did not differ in terms of sex

Table 1 Baseline characteristics of patient groups dichotomized by left atrial pressure and left ventricular end-diastolic pressure

	LA pressure < 15 mmHg	LA pressure ≥ 15 mmHg	*P*	LVEDP < 16 mmHg	LVEDP ≥ 16 mmHg	*P*
n	59	104	—	80	97	—
Patient characteristics and medical history						
Age	78.5 (±7.2)	79.1 (±6.7)	0.59	80.0 (±7.0)	78.8 (±6.3)	0.21
Female gender	31 (52.5%)	53 (51.0%)	0.85	37 (46.3%)	51 (52.6%)	0.4
Body mass index (kg/m^2)	25.3 (±4.7)	25.8 (±4.2)	0.48	24.9 (±4.0)	25.9 (±4.8)	0.13
Arterial hypertension	49 (83.1%)	83 (79.8%)	0.61	67 (83.8%)	80 (82.5%)	0.82
Diabetes mellitus	10 (17.0%)	13 (14.3%)	0.48	8 (10.0%)	20 (20.6%)	0.05
Coronary artery disease	44 (74.6%)	67 (64.4%)	0.62	52 (65.0%)	66 (68.0%)	0.67
Atrial fibrillation	**36 (61.0%)**	**82 (78.8%)**	**0.04**	54 (67.5%)	73 (75.3%)	0.25
History of stroke	7 (11.9%)	9 (8.7%)	0.51	10 (12.5%)	9 (9.3%)	0.49
COPD	8 (13.6%)	16 (15.4%)	0.75	11 (13.8%)	13 (13.4%)	0.95
Blood tests and scores						
Baseline creatinine (μmol/L)	123.2 (±59.8)	120.0 (±48.7)	0.71	110.9 (±37.9)	125.3 (±58.5)	0.06
Baseline haemoglobin (mg/dL)	12.2 (±1.9)	12.1 (±1.7)	0.83	12.2 (±1.8)	12.0 (±1.9)	0.4
Baseline Troponin T (ng/L)	33.7 (±23.1)	39.8 (±42.5)	0.39	29.3 (±22.3)	39.9 (±40.5)	0.08
Baseline NT-proBNP (pg/mL)	3071.7 (±4170.0)	5544.9 (±7511.3)	0.06	3230.3 (±3353.2)	5061.0 (±7106.1)	0.08
Baseline NYHA class	3.1 (±0.7)	3.2 (±0.6)	0.31	3.1 (±0.7)	3.1 (±0.6)	0.74
EuroScore II	7.1 (±6.9)	6.9 (±7.1)	0.8	7.2 (±7.0)	6.1 (±6.9)	0.31
STS score	4.3 (±4.2)	4.0 (±3.3)	0.61	4.5 (±4.8)	4.2 (±3.9)	0.57
H_2FPEF score	**4.3 (±2.1)**	**5.1 (±1.9)**	**0.02**	**4.3 (±1.7)**	**5.1 (±2.1)**	**0.006**
Echocardiographic parameters						
LVEF (%)	62.1 (±7.2)	63.7 (±8.9)	0.3	62.6 (±7.5)	63.5 (±9.2)	0.51
LVEDd (mm)	53.8 (±7.2)	54.1 (±8.0)	0.79	54.0 (±7.7)	53.4 (±7.9)	0.64
LA diameter (mm)	53.1 (±7.2)	55.9 (±9.9)	0.09	55.7 (±10.1)	53.8 (±7.9)	0.2
IVSd (mm)	11.2 (±2.4)	11.2 (±2.2)	0.95	11.0 (±2.4)	11.4 (±2.0)	0.26
LVPWd (mm)	10.9 (±2.1)	11.3 (±1.9)	0.31	10.8 (±2.1)	11.4 (±1.9)	0.11
MR severity >II°	52 (89.7%)	90 (88.2%)	0.78	72 (91.1%)	82 (85.4%)	0.24
MS severity >I°	0 (0%)	2 (2.0%)	0.28	1 (1.3%)	1 (1.1%)	0.88
Functional MR	22 (50.0%)	22 (50.0%)	1.0	18 (37.5%)	30 (62.5%)	0.23
Grade of TR	1.9 (±0.9)	2.2 (±0.9)	0.08	2.0 (±0.9)	2.0 (±0.9)	0.9
TAPSE	**21.1 (±5.4)**	**19.8 (±5.4)**	**0.15**	**20.1 (±4.9)**	**20.7 (±5.4)**	**0.42**
Haemodynamic parameters						
Mean LA pressure (mmHg)	**12.4 (±5.6)**	**22.6 (±16.3)**	**<0.001**	**15.5 (±7.5)**	**21.1 (±17.3)**	**0.01**
LA v-wave (mmHg)	**22.5 (±10.6)**	**37.3 (±16.1)**	**<0.001**	**26.8 (±13.5)**	**35.5 (±17.5)**	**<0.0001**
LVEDP (mmHg)	**16.0 (±6.3)**	**18.8 (±6.2)**	**0.008**	**12.2 (±3.1)**	**22.1 (±5.3)**	**<0.0001**
Mean RA pressure	**7.5 (±5.2)**	**12.5 (±6.1)**	**<0.001**	**9.3 (±5.7)**	**12.8 (±7.0)**	**0.002**
sPAP (mmHg)	**42.3 (±14.8)**	**56.2 (±15.6)**	**<0.001**	**47.7 (±14.6)**	**54.1 (±17.3)**	**0.02**
mPAP (mmHg)	**26.3 (±9.6)**	**36.4 (±10.3)**	**<0.001**	**29.7 (±9.9)**	**35.2 (±11.3)**	**0.004**
PVR (dyn × s × cm^{-5})	**246.2 (±176.9)**	**424.8 (±325.5)**	**0.02**	**241.1 (±156.6)**	**411.7 (±326.4)**	**0.04**
Cardiac index (L/min/m^2)	**2.3 (±0.6)**	**2.0 (±0.5)**	**0.04**	**2.2 (±0.5)**	**2.1 (±0.6)**	**0.13**
Periprocedural events						
Death within 30 days	1 (2.0%)	3 (3.1%)	0.68	1 (1.4%)	3 (3.3%)	0.44
Need for CPR	0 (0%)	1 (1.0%)	0.45	1 (1.3%)	1 (1.0%)	0.89
Need for catecholamines	5 (8.5%)	11 (10.6%)	0.66	7 (8.8%)	8 (8.3%)	0.9

COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; IVSd, interventricular septum diameter; LA diameter, left atrial diameter; LVEDd, left ventricular end-diastolic diameter; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall diameter; mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MS, mitral stenosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RA pressure, right atrial pressure; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation. Significant values are marked in bold.

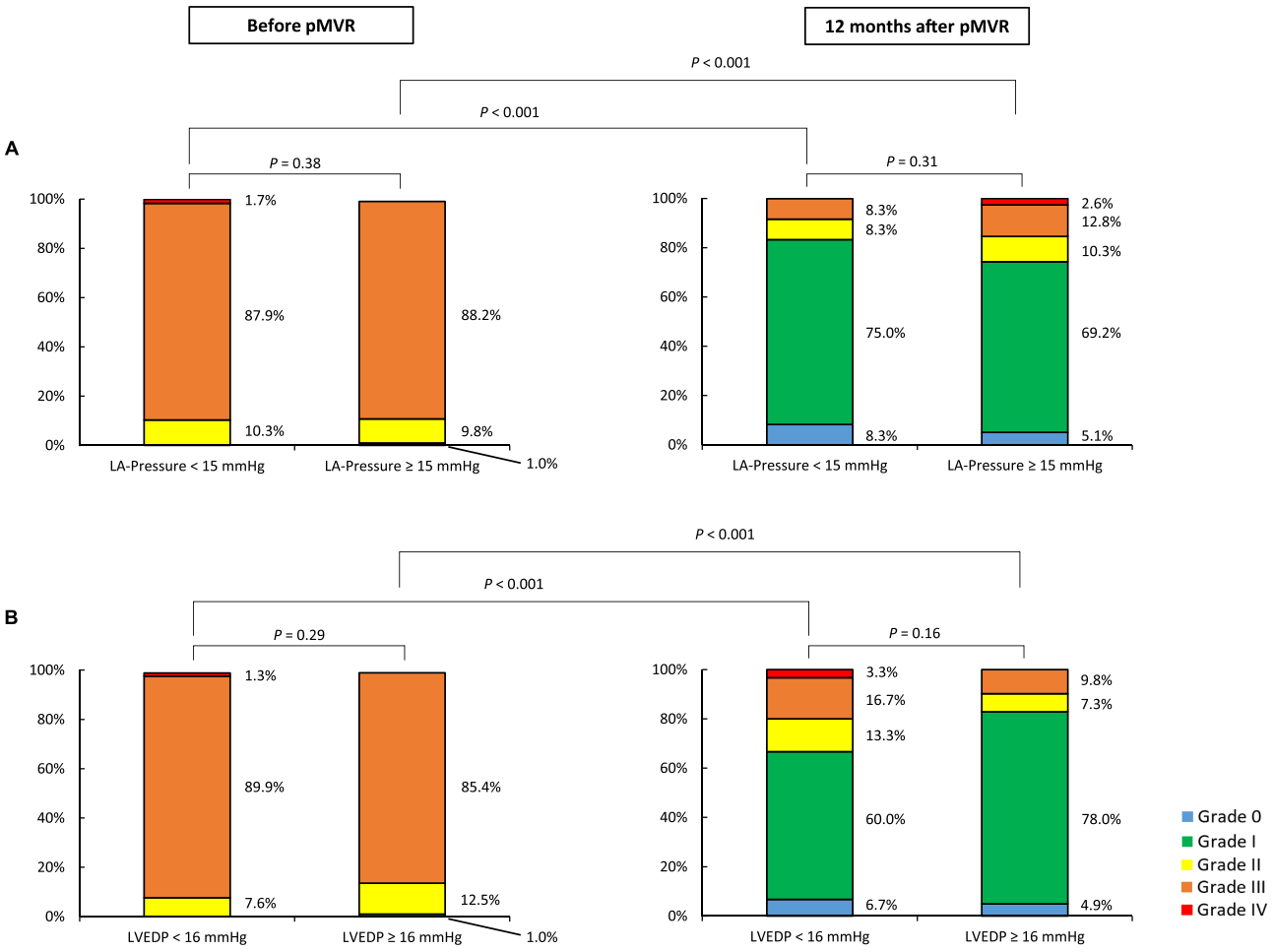
and body mass index (BMI) as well as prevalence of diabetes mellitus or arterial hypertension. As expected, the prevalence of AF was significantly higher in the elevated LAP group (78.8% vs. 61.0%, $P = 0.04$). Troponin T and NT-proBNP levels were insignificantly elevated in the high LAP group (Troponin T: 39.8 vs. 33.7 ng/L, $P = 0.39$; NT-proBNP: 5544.9 vs. 3071.7 pg/mL, $P = 0.06$). The H_2FPEF score indicating diagnostic probability for HFpEF was significantly higher in the elevated LAP group (5.1 vs. 4.3, $P = 0.02$). LVEDP, right atrial (RA) pressure, systolic pulmonary artery pressure (sPAP), mean pulmonary artery pressure (mPAP), PCWP, and pulmonary vascular resistance (PVR) each were significantly elevated in patients with higher LAP (*Table 1*).

Ninety-seven patients (55%) had elevated LVEDP levels (≥16 mmHg), while 80 patients (45%) showed normal LVEDP (<16 mmHg). The number of female patients (52.6% vs. 46.3%, $P = 0.4$) and BMI (25.9 vs. 24.9, $P = 0.13$) were numerically higher in patients with elevated LVEDP, as was the prevalence of AF (75.3% vs. 67.5%, $P = 0.25$) and diabetes mellitus, closely missing statistical significance (20.6% vs. 10.0%, $P = 0.05$). Accordingly, the H_2FPEF score was significantly higher (5.1 vs. 4.3, $P = 0.006$). Troponin T and NT-proBNP levels were also distinctively, yet insignificantly, elevated in this group (Troponin T: 39.9 vs. 29.3 ng/L, $P = 0.08$; NT-proBNP: 5061.0 vs. 3230.3 pg/mL, $P = 0.08$). Furthermore, LAP, RA pressure, sPAP, mPAP, and PVR were significantly higher. Baseline characteristics of the LAP and LVEDP groups are shown in *Table 1*. Baseline characteristics of patients with both elevated LAP and LVEDP are shown in the Supporting Information, *Table S1*.

Procedural outcome—mitral regurgitation grade reduction

A total of 89.8% of patients with normal LAP and 88.2% of patients with elevated LAP had grade III or IV MR. The number of patients with grade III or IV MR could be reduced to 8% in

Figure 1 Mitral regurgitation grade distribution before and 12 months after percutaneous edge-to-edge mitral valve repair (pMVR) in left atrial (LA) pressure (A) and left ventricular end-diastolic pressure (LVEDP) (B) collectives.



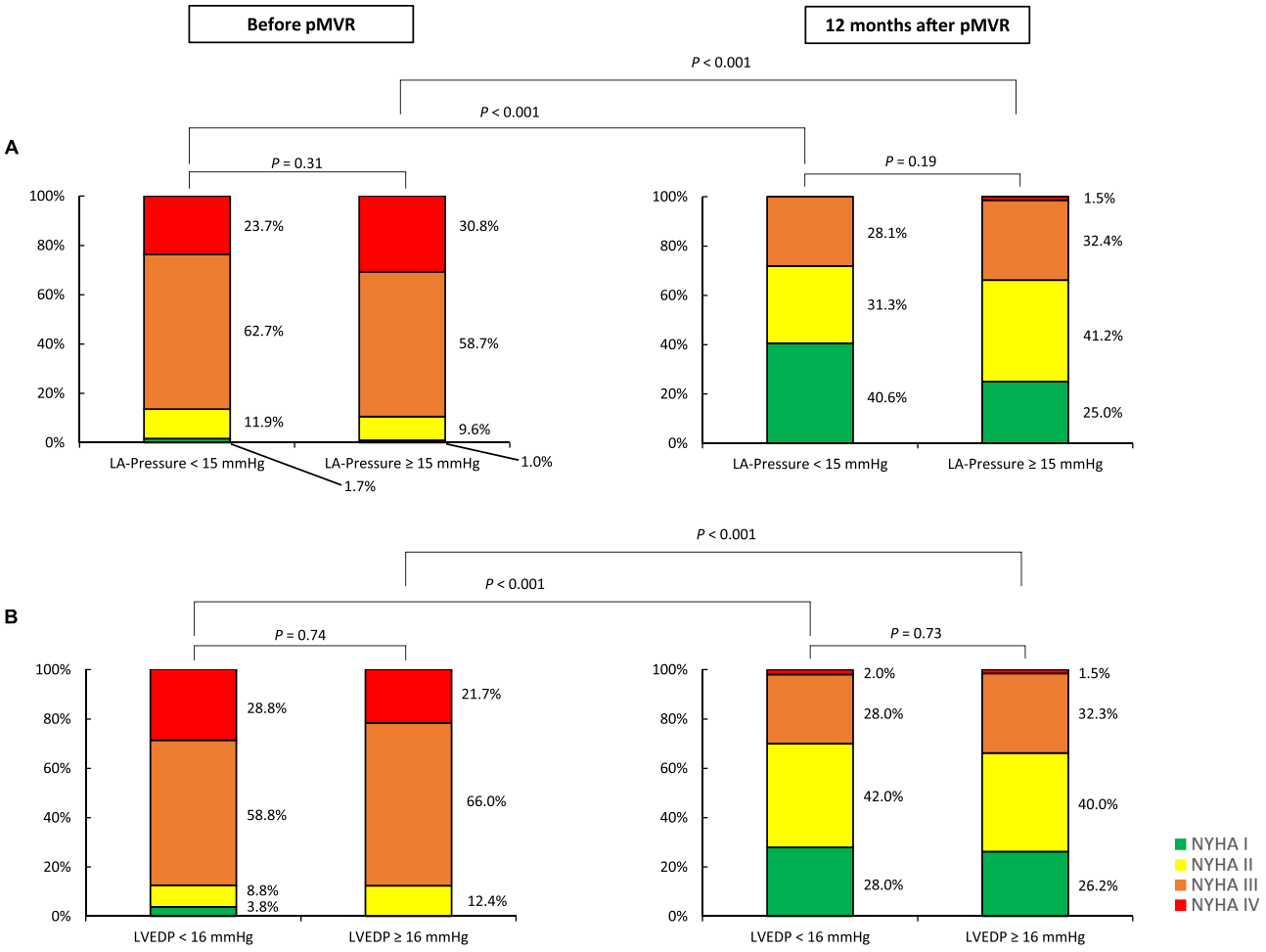
the normal LAP group ($P < 0.001$) and to 15% in the elevated LAP group ($P < 0.001$). A total of 91.4% of patients with normal LVEDP and 85.4% with elevated LVEDP had grade III or IV MR. pMVR could reduce the number of patients with grade III or IV MR to 20% in the normal LVEDP group ($P < 0.001$) and to 10% in the elevated LVEDP group ($P < 0.001$). In summary, MR grade reduction was efficient in both elevated and normal pressure groups. The procedural results regarding MR grade reduction are shown in *Figure 1*.

Procedural outcome—New York Heart Association class reduction, biomarkers, and heart failure-induced hospital admissions

Eighty-six per cent of patients with normal LAP and 89% of patients with elevated LAP had dyspnoea equivalent to an NYHA class of III or IV before pMVR. Twelve months after the procedure, the number of patients with NYHA classes III and IV was reduced significantly to 28% ($P < 0.001$) and 34% ($P < 0.001$), respectively. In a paired analysis, NT-proBNP levels decreased insignificantly [normal LAP group: 3277.6 to 2500.1 pg/mL ($P = 0.28$), elevated LAP group: 6530.4 to 5456.7 pg/mL ($P = 0.21$), P for post-pMVR comparison = 0.07]. Importantly, the total number of HF-induced hospitalizations in the 12 months following pMVR could be reduced significantly compared with 12 months before the procedure (normal LAP group: 8 vs. 49 hospitalizations, $P < 0.001$; elevated LAP group: 12 vs. 69 hospitalizations, $P < 0.001$). Creatinine levels rose irrespective of LAP (164.3 vs. 127.9 μmol/L, $P = 0.09$).

Pre-treatment NYHA class III or IV occurred equally in 88% of patients with normal and elevated LVEDP. Significant reduction of dyspnoea could be achieved in both groups, and the number of patients with NYHA class III or IV 12 months after pMVR was 30% in the normal LVEDP group ($P < 0.001$) and 34% in the elevated LVEDP group ($P < 0.001$). In a paired analysis, NT-proBNP levels decreased

Figure 2 New York Heart Association (NYHA) class before and 12 months after percutaneous edge-to-edge mitral valve repair (pMVR) in left atrial (LA) pressure (A) and left ventricular end-diastolic pressure (LVEDP) (B) collectives.



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insignificantly after 12 months [normal LVEDP group: 3780.7 to 3392.2 pg/mL (P = 0.56), elevated LVEDP group: 5840.2 to 4510.1 pg/mL (P = 0.09), P for post-pMVR comparison = 0.6]. HF-induced hospitalizations could be reduced significantly (normal LVEDP group: 5 vs. 61 hospitalizations, $P < 0.001$; elevated LVEDP group: 17 vs. 75 hospitalizations, $P < 0.001$). Creatinine levels increased significantly in both groups (143.4 and 188.4 μmol/L, P = 0.001). The procedural results are shown in *Figures 2* and *3*.

Twelve-month outcome—mortality, major adverse cardiac and cerebrovascular events, and rehospitalization

Thirty-day mortality was 3.1% in patients with elevated LAP and 3.3% in patients with elevated LVEDP. After a 12 month follow-up, all-cause and cardiovascular mortality was 20% in patients with normal LAP and 15% in patients with high LAP (P = 0.31). Similar results were observed in the normal LVEDP (all-cause and cardiovascular mortality of 16%) and high LVEDP groups (all-cause and cardiovascular mortality of 16%, P = 0.81). These findings are demonstrated in *Figure 4A* and *4B*.

Major adverse cardiac and cerebrovascular event occurred in 15 patients with normal LAP and in 30 patients with high LAP (26% vs. 30%, P = 0.58). MACCE was observed in 18 patients with normal LVEDP and in 31 patients with high LVEDP (23% vs. 33%, P = 0.17) (*Figure 4C*). Five patients with normal LAP and nine patients with high LAP (14% vs. 12%, P = 0.79) were rehospitalized due to HF. Rehospitalization occurred significantly less often in the normal LVEDP group [3 patients (5%)] compared with the high LVEDP group [12 patients (16%), P = 0.049] (*Figure 4D*). Similar, yet statistically insignificant, results were obtained after limiting data analysis to patients with FMR (12 month rehospitalization in the normal vs. elevated LVEDP group: 0% vs. 23.81%, P = 0.06; Supporting Information, *Figure S1*). No significant difference in outcome was seen regarding patients with simultaneously elevated LAP and LVEDP (Supporting Information, *Table S1* and *Figure S2*).

Univariate Cox regression analysis identified baseline Troponin T and LVEDP as significantly ($P < 0.05$) and NT-proBNP as probably ($P < 0.1$) associated with higher risk of HF-induced rehospitalization (*Table 2*). However, in multivariate Cox regression analysis including those three variables, the regular LVEDP cut-off of ≥16 mmHg failed to predict HF-induced rehospitalization [hazard ratio (HR) 2.971, 95% confidence interval (CI) 0.628–14.042, P = 0.073] (*Table 3*). Through ROC analysis and Youden's J statistic (*Table 4*), the two best sensitivity/specificity proportions for prediction of HF-induced rehospitalization occurred for LVEDP cut-offs of ≥16 mmHg (sensitivity 78.6%, specificity 46.0%, J 0.246) and ≥25 mmHg (sensitivity 35.7%, specificity 91.3%, J 0.269). Therefore, a second multivariate Cox regression analysis including Troponin T, NT-proBNP, and the alternative ≥25 mmHg cut-off was carried out (*Table 5*). In this analysis, LVEDP ≥ 25 mmHg was significantly associated with a higher risk for rehospitalization due to worsening of HF (HR 4.073, 95% CI 1.078–15.384, P = 0.038).

Discussion

Heart failure with preserved ejection fraction has emerged as a highly relevant phenomenon. Roughly 5% of the population aged 60 and older were identified with HFpEF.[9] However, the condition is still notoriously underdiagnosed.[13] MR is a frequent feature of HFpEF and can lead to a further

Figure 3 Total number of hospital admissions due to heart failure before and after percutaneous edge-to-edge mitral valve repair (pMVR) in normal and elevated left atrial (LA) pressure groups (A) and normal and elevated left ventricular end-diastolic pressure (LVEDP) groups (B).

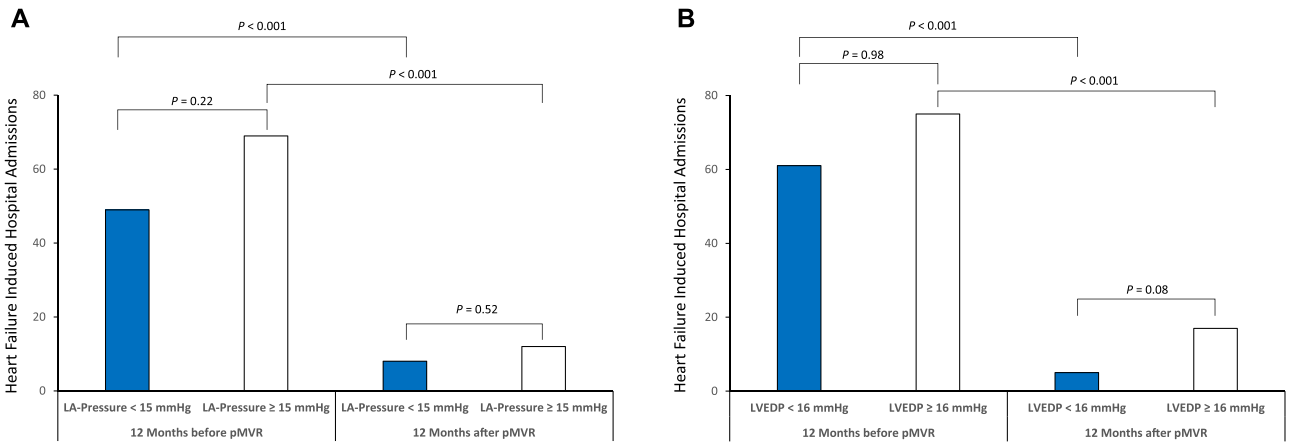

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Figure 4 Twelve-month outcome of percutaneous edge-to-edge mitral valve repair patients with preserved left ventricular ejection fraction and normal or elevated left atrial pressure (LAP) (left column) and left ventricular end-diastolic pressure (LVEDP) levels (right column). (A) All-cause mortality, (B) cardiovascular mortality, (C) major adverse cardiac and cerebrovascular events (MACCE), and (D) rehospitalization due to worsening of heart failure. Red line: LAP $<$ 15 mmHg/LVEDP $<$ 16 mmHg. Blue line: LAP $\geq$ 15 mmHg/LVEDP $\geq$ 16 mmHg.

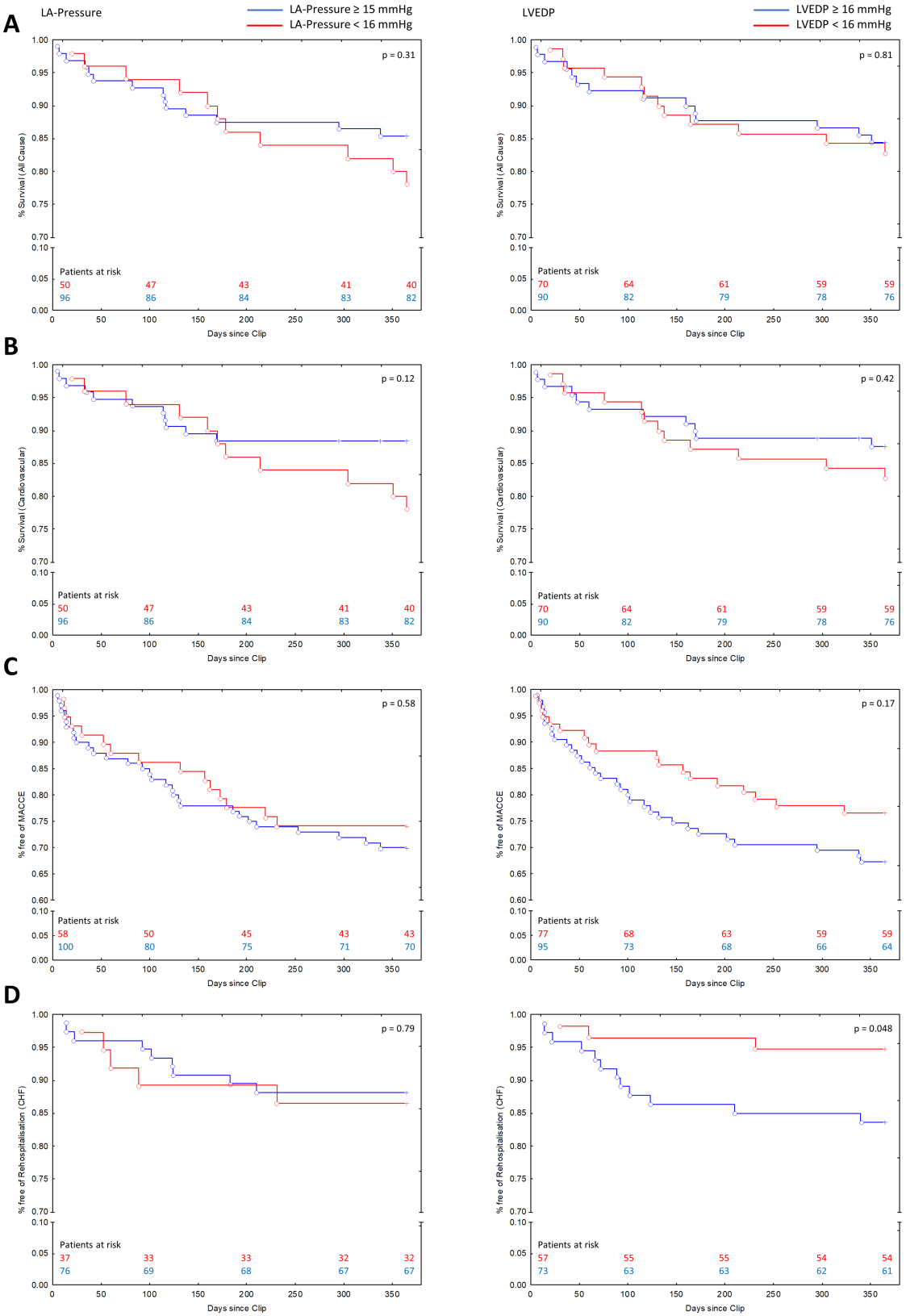

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Table 2 Univariate Cox regression analysis for prediction of 12 month rehospitalization due to worsening of heart failure

Variable	*P*	Hazard ratio	95% confidence interval
Age	0.841	0.992	0.921–1.069
Sex	0.254	1.784	0.660–4.825
Body mass index	0.611	1.025	0.928–1.136
Arterial hypertension	0.498	1.473	0.480–4.519
Diabetes mellitus	0.547	1.581	0.361–6.912
Coronary artery disease	0.234	1.782	0.688–4.620
Atrial fibrillation	0.285	0.507	0.146–1.763
Stroke	0.719	1.449	0.192–10.928
COPD	0.297	25.106	0.059–10 755.274
Baseline creatinine	0.427	1.002	0.997–1.007
Baseline haemoglobin	0.272	1.175	0.881–1.565
Baseline Troponin T	**0.03**	**1.009**	**1.001–1.017**
Baseline NT-proBNP	**0.081**	**1.000**	**1.000–1.000**
NYHA class	0.545	0.778	0.394–1.537
EuroScore II	0.545	0.967	0.868–1.077
STS score	0.913	0.994	0.889–1.111
H_2FPEF score	0.162	1.189	0.933–1.516
LVEF	0.331	1.028	0.972–1.087
LVED diameter	0.412	1.028	0.963–1.097
LA pressure	0.927	1.002	0.970–1.034
LA diameter	0.152	1.033	0.988–1.079
IVS	0.938	1.010	0.793–1.285
LVPW	0.730	0.953	0.726–1.252
MR grade >II	0.378	0.402	0.053–3.045
MS grade >I	0.320	20.305	0.000–3.913e12
LVEDP	**0.006**	**1.103**	**1.029–1.183**
Functional MR	0.538	0.663	0.180–2.450
TR grade	0.555	1.204	0.649–2.233
LA v-wave	0.159	1.022	0.991–1.054
sPAP	0.724	1.006	0.973–1.040
mPAP	0.794	1.007	0.957–1.059
PVR	0.850	1.000	0.998–1.003
Cardiac index	0.893	0.959	0.518–1.773

COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; IVS, interventricular septum (diastolic); LA, left atrial; LVED, left ventricular end-diastolic; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior wall (diastolic); mPAP, mean pulmonary artery pressure; MR, mitral regurgitation; MS, mitral stenosis; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; TR, tricuspid regurgitation. Significant values are marked in bold.

Table 3 Multivariate analysis including baseline Troponin T, N-terminal pro-brain natriuretic peptide, and left ventricular end-diastolic pressure ≥ 16 mmHg for prediction of 12 month rehospitalization due to worsening of heart failure

Variable	*P*	Hazard ratio	95% confidence interval
Troponin T	0.257	1.010	0.993–1.026
NT-proBNP	0.692	1.000	1.000–1.000
LVEDP ≥ 16 mmHg	0.170	2.971	0.628–14.042

LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide.

worsening of symptoms, increased readmission rates, and even mortality.[6,7] pMVR has been established as a therapeutical option for patients with moderate to severe MR especially in heart failure with reduced EF (HFrEF) patients. Studies evaluating the effect of pMVR in HFpEF patients are sparse.

While scoring systems such as the H_2FPEF score are easy to apply to identify potential HFpEF candidates, a multistep diagnostic approach as suggested by Pieske *et al*. includes invasive haemodynamic measurements such as LVEDP and PCWP/LAP to account for the complex pathophysiological hallmarks of this disease. Therefore, the aim of our study was to examine patients with preserved EF who underwent pMVR regarding their functional outcome dependent on normal or elevated LAP or LVEDP, indicating HFpEF.

Table 4 Receiver operating characteristic analysis of left ventricular end-diastolic pressure cut-off values for prediction of 12 month rehospitalization due to worsening of heart failure

LVEDP ≥	Sensitivity	1 − Specificity	Specificity	*J*
5.0	1.000	1.000	0.000	0.000
6.5	1.000	0.982	0.018	0.018
7.5	1.000	0.965	0.035	0.035
8.5	1.000	0.947	0.053	0.053
9.5	1.000	0.876	0.124	0.124
10.5	1.000	0.832	0.168	0.168
11.5	1.000	0.779	0.221	0.221
12.5	0.929	0.743	0.257	0.186
13.5	0.929	0.717	0.283	0.212
14.5	0.857	0.664	0.336	0.193
15.5	0.786	0.549	0.451	0.237
16.5	0.786	0.540	0.460	0.246
17.5	0.500	0.469	0.531	0.031
18.5	0.500	0.426	0.574	0.074
19.5	0.429	0.354	0.646	0.075
20.5	0.357	0.212	0.788	0.145
21.5	0.357	0.177	0.823	0.180
22.5	0.357	0.150	0.850	0.207
23.5	0.357	0.133	0.867	0.224
25.0	0.357	0.088	0.912	0.269
26.5	0.214	0.062	0.938	0.152
28.0	0.214	0.053	0.947	0.161
30.0	0.143	0.027	0.973	0.116
32.0	0.143	0.018	0.982	0.125
33.5	0.143	0.009	0.991	0.134
37.5	0.071	0.000	1.000	0.071
42.0	0.000	0.000	1.000	0.000

J, Youden's *J* or Youden's index (*J* = sensitivity + specificity − 1); LVEDP, left ventricular end-diastolic pressure.

Table 5 Multivariate analysis including baseline Troponin T, N-terminal pro-brain natriuretic peptide, and left ventricular end-diastolic pressure ≥ 25 mmHg for prediction of 12 month rehospitalization due to worsening of heart failure

Variable	*P*	Hazard ratio	95% confidence interval
Troponin T	0.590	1.005	0.986–1.025
NT-proBNP	0.888	1.000	1.000–1.000
LVEDP ≥ 25 mmHg	**0.038**	**4.073**	**1.078–15.384**

LVEDP, left ventricular end-diastolic pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide. Significant values are marked in bold.

Baseline characteristics and typical heart failure with preserved ejection fraction features

While there were certain differences in the clinical characteristics of the patients in the elevated compared with the normal LAP group—patients were older, had a higher BMI, and AF was more frequent—the elevated LVEDP group comprised a typical HFpEF collective[14]: a higher proportion of female patients, higher average BMI, and higher prevalences of diabetes (all non-significant) and AF (statistically significant). Coronary artery disease as a potential confounder of worsening HF, MACCE, or death was present in similar proportions in both groups. Flow-limiting coronary artery stenosis had been ruled out before pMVR. NT-proBNP and Troponin T values were insignificantly, yet considerably, higher in patients with elevated filling pressures. Both NT-proBNP and high-sensitive Troponin T have been characterized as negative prognostic markers for the outcome of hospitalized HFpEF patients.[15,16] In a large analysis, elevated troponin levels occurred in 23% of patients with decompensated HFpEF and were associated with higher odds of in-hospital mortality, greater length of stay, mortality, and 30 day readmission.[17] Moreover, in biomarker studies regarding pMVR in a mixed patient group comprising HFpEF and HFrEF, even moderately increased Troponin T levels of $>$21 ng/mL were predictive of a higher hospital readmission rate after treatment.[10] In our study, univariate regression analysis showed a similar effect in a pure HFpEF collective. Troponin T was significantly ($P < 0.05$) and NT-proBNP was probably ($P < 0.1$) associated with a higher risk of HF-induced rehospitalization. Multivariate Cox regression however could not confirm either of the two as an independent predictor in this cohort. Of note, follow-up NT-proBNP levels were not measured as part of the study routine and were mainly taken from rehospitalized patients. Interpretation of the paired analysis (NT-proBNP levels pre vs. post pMVR) therefore requires consideration of a possible selection bias.

In the high LVEDP group, a strong elevation of baseline creatinine could be observed. Worsening renal function has been shown to be a frequent feature of all types of HF, especially HFpEF. Its occurrence is a manifestation of a more compromised clinical status and has been linked to subsequent long-term mortality.[18] Remarkably, creatinine levels increased in all patient groups over 12 months. The underlying mechanisms for this effect are unclear, because worsening of HF occurred less often after pMVR. A natural decrease in renal function was to be expected due to the high age and comorbidities of the patients in our study. Secondly, creatinine measurements were not carried out in all patients as part of the study protocol. Therefore, the probability of a selection bias (patients with known progressing impairment of renal function or rehospitalization for renal or HF) is high. Nonetheless, further studies are necessary to investigate the course of renal function after pMVR in HFpEF patients.

The H_2FPEF score indicating diagnostic probability for HFpEF was significantly higher in both elevated LAP and LVEDP groups. While limitations such as lack of generalizability due to the underlying single-centre study and missing external validation are overt, this score has already been discussed as a predictor of adverse outcome in HFpEF.[19]

Systolic pulmonary artery pressure, mPAP, and PVR were strongly elevated in patients with higher LVEDP or LAP. These striking results are indicative of consecutive pulmonary hypertension, a negative effect of persistent HF. These data argue in favour of adequate patient selection. It is known that an acute increase of LVEDP and LAP levels in the context of HFpEF can lead to stress failure of the pulmonary capillaries and alveolar membrane and results in pulmonary oedema and dyspnoea.[20] Whereas the occurrence of pulmonary hypertension is a clear sign of severe haemodynamic impairment through LAP elevation, the underlying cause of increased pressure levels in our cohort is hard to distinguish. Diastolic ventricular dysfunction and MR can amplify each other's effect on increasing LAP, and adjusted LA pressure cut-offs in MR patients have not been defined yet. Preferring LVEDP instead of LAP measurement to diagnose HFpEF in a setting of MR might be appropriate. Similar mechanisms exist for RA pressure, because the right ventricle is also affected by diastolic dysfunction. While tricuspid annular plane systolic excursion did not differ relevantly between groups, RA pressure was significantly elevated to 13 mmHg in patients with high LAP or LVEDP, as described before for HFpEF patients.[21,22] Nonetheless, RA pressure levels were not as high as would be expected during excessive fluid overload. Mean tricuspid regurgitation grade did not differ significantly between groups. While fluid retention as a cause of elevated filling pressures cannot be ruled out completely, all patients underwent a diuretic scheme in order to achieve a clinically euvolaemic state. More likely, the elevated right heart filling pressures occur as a result of higher pulmonary artery pressures and haemodynamic compromise due to HFpEF.

Finally, 30 day mortality was lower than expected by EuroScore II and Society of Thoracic Surgeons (STS), yet comparable with previously published MitraClip cohorts irrespective of LVEF.[23–25] It has been discussed previously that STS and EuroScore II are prone to overestimation of 30 day mortality.[26,27]

Mitral regurgitation grade and symptom reduction by percutaneous edge-to-edge mitral valve repair after 12 months was independent of left atrial pressure and left ventricular end-diastolic pressure levels

Before treatment, most patients suffered from moderate to severe MR. The number of patients presenting with severe

(grade IV) MR was considerably lower compared with studies involving HFrEF patients, for example, the COAPT trial.[3]

Aetiology of MR was mostly degenerative or prolapse of the mitral valve. FMR occurred less often; however, it was distinctively more frequent in patients with elevated LVEDP. This finding is in accordance with opinions in current literature, which are linking the development of MR to pathologic atrial remodelling in the absence of degeneration or LV systolic dysfunction (atrial FMR).[4,5] Studies have found a prevalence of up to 7% in patients with lone AF and up to 53% in HFpEF.[4]

Significant MR grade reduction could be achieved in most cases regardless of filling pressure levels. Our data show that this device success leads to successful symptom reduction. Pre-treatment NYHA class was similar in all patient groups. Dyspnoea on exertion and—importantly—hospitalizations for worsening of HF could be reduced significantly in patients with both normal and elevated filling pressures. To our knowledge, this is the first set of data demonstrating the efficacy of pMVR to alleviate HF symptoms in an HFpEF collective. Recent pharmacotherapy trials for HFpEF failed to prove efficacy. For instance, in the most recent PARAGON trial, Sacubitril/Valsartan, which is successfully used for treatment of HFrEF, could not significantly reduce hospitalizations for HF or cardiovascular death in a large HFpEF patient collective.[28] Furthermore, Candesartan[29] and Spironolactone[30] have failed to prove efficacy so far.

Elevated left ventricular end-diastolic pressure levels predict higher risk for rehospitalization

No significant difference could be seen between all groups concerning all-cause and cardiovascular mortality, as well as MACCE. However, rehospitalization for decompensation of HF has been considered an equally important parameter in recent HFpEF studies. Strikingly, a significant increase of HF-induced rehospitalizations of 11% could be seen in patients presenting with elevated LVEDP levels. Similar results, however restricted by small sample size, were obtained for patients with sole atriogenic FMR. No significant difference was seen in patients with both elevated LAP and LVEDP. Larger patient cohorts are necessary to improve conclusiveness.

Pieske *et al*. suggested an LVEDP cut-off level of ≥16 mmHg to reach a definite HFpEF diagnosis in HF patients.[9] Through ROC analysis, we could confirm the optimal sensitivity/specificity proportion (Youden's index) for the prediction of rehospitalization for this cut-off in our pMVR cohort. However, multivariate Cox regression analysis including Troponin T, NT-proBNP, and LVEDP ≥ 16 mmHg could not confirm the latter as an independent predictor for HF rehospitalization. When using a higher LVEDP cut-off of ≥25 mmHg, for which the second highest Youden's index was calculated, multivariate Cox regression analysis resulted in a significant four-fold increase of risk for rehospitalization due to worsening of HF. These data suggest that, while the use of the ≥16 mmHg cut-off is suitable for diagnosis of HFpEF, a higher cut-off of ≥25 mmHg can be used as a predictor of 12 month rehospitalization of HFpEF patients undergoing pMVR.

Study limitations

These data resemble a single-centre experience and a retrospective cohort study. Although short-term procedure-associated complications were very rare, patient outcome is dependent on a small number of operating physicians at our centre and generalizability of our data is therefore limited. Furthermore, the size of our patient collective was small. Larger as well as external cohorts should provide further validation of our data. Moreover, echocardiographic assessment and classification were carried out at our centre without the use of an independent core laboratory.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. 12 month outcome of MitraClip patients with preserved LV-EF, atriogenic MR and normal or elevated LA-Pressure and LVEDP levels. A all cause mortality B cardiovascular mortality C MACCE D rehospitalisation due to worsening of heart failure.

Figure S2. 12 month outcome of MitraClip patients with preserved LV-EF and both normal or both elevated LA-Pressure and LVEDP levels. A all cause mortality B cardiovascular mortality C MACCE D rehospitalisation due to worsening of heart failure.

Table S1. Baseline characteristics of patients with both normal or both elevated LA-Pressure and LVEDP.

COPD: chronic obstructive pulmonary disease; NT-proBNP: N-terminal pro brain natriuretic peptide; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; LV-EF: left ventricular ejection fraction; LVEDd: left ventricular end-diastolic diameter; LA-Diameter: left atrial diameter; IVSd: interventricular septum diameter; LVPWd: left ventricular posterior wall diameter; MR: mitral regurgitation; MS: mitral stenosis; TR: tricuspid regurgitation; LVEDP: left ventricular end-diastolic pressure; RA-Pressure: right atrial pressure; sPAP: systolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; CPR: cardiopulmonary resuscitation

References

1. Treede H, Charitos EI. The role of transcatheter mitral valve therapy in heart failure. *Eur J Cardiothorac Surg* 2019; **55**: i26–i30.
2. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Munoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017; **38**: 2739–2791.
3. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, Whisenant B, Grayburn PA, Rinaldi M, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Marx SO, Cohen DJ, Weissmann NJ, Mack MJ. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379**: 2307–2318.
4. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, Vandervoort PM. Atrial functional mitral regurgitation: *JACC* Review Topic of the Week. *J Am Coll Cardiol* 2019; **73**: 2465–2476.
5. Silbiger J. Mechanistic insights into atrial functional mitral regurgitation: far more complicated than just left atrial remodeling. *Echocardiography* 2019; **36**: 164–169.
6. Tamargo M, Obokata M, Reddy YNV, Pislaru SV, Lin G, Egbe AC, Nishimura RA, Borlaug BA. Functional mitral regurgitation and left atrial myopathy in heart failure with preserved ejection fraction. *Eur J Heart Fail* 2020; **22**: 489–498.
7. Kajimoto K, Sato N, Takano T, Investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Functional mitral regurgitation at discharge and outcomes in patients hospitalized for acute decompensated heart failure with a preserved or reduced ejection fraction. *Eur J Heart Fail* 2016; **18**: 1051–1059.
8. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018; **138**: 861–870.
9. Pieske B, Tschöpe C, de Boer RA, Fraser AG, Anker SD, Donal E, Edelmann F, Fu M, Guazzi M, Lam CSP, Lancellotti P, Melenovsky V, Morris DA, Nagel E, Pieske-Kraigher E, Ponikowski P, Solomon SD, Vasan RS, Rutten FH, Voors AA, Ruschitzka F, Paulus WJ, Seferovic P, Filippatos G. How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020; **22**: 391–412.
10. Keßler M, Seeger J, Muche R, Wöhrle J, Rottbauer W, Markovic S. Predictors of rehospitalization after percutaneous edge-to-edge mitral valve repair by MitraClip implantation. *Eur J Heart Fail* 2018; **21**: 182–192.
11. Stone GW, Adams DH, Abraham WT, Kappetein AP, Genereux P, Vranckx P, Mehran R, Kuck K, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS, Mitral Valve Academic Research Consortium (MVARC). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol* 2015; **66**: 308–321.
12. Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, St. Goar F, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Condado JA, Foster E. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 2005; **46**: 2134–2140.
13. Deaton C, Benson J. Time for correct diagnosis and categorisation of heart failure in primary care. *Br J Gen Pract* 2016; **66**: 554–555.
14. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016; **37**: 2129–2200.
15. Suzuki S, Motoki H, Minamisawa M, Okuma Y, Shoin W, Okano T, Kimura K, Ebisawa S, Okada A, Kuwahara K. Prognostic significance of high-sensitive cardiac troponin in patients with heart failure with preserved ejection fraction. *Heart Vessels* 2019; **34**: 1650–1656.
16. Salah K, Stienen S, Pinto YM, Eurlings LW, Metra M, Bayes-Genis A, Verdiani V, Tijssen JGP, Kok WE. Prognosis and NT-proBNP in heart failure patients with preserved versus reduced ejection fraction. *Heart* 2019; **105**: 1182–1189.
17. Pandey A, Golwala H, Sheng S, DeVore AD, Hernandez AF, Bhatt DL, Heidenreich PA, Yancy CW, de Lemos JA, Fonarow GC. Factors associated with and prognostic implications of cardiac troponin elevation in decompensated heart failure with preserved ejection fraction: findings from the American Heart Association Get With The Guidelines-Heart Failure program. *JAMA Cardiol* 2017; **2**: 136–145.
18. Löfman I, Szummer K, Evans M, Carrero JJ, Lund LH, Jernberg T. Incidence of, associations with and prognostic impact of worsening renal function in heart failure with different ejection fraction categories. *Am J Cardiol* 2019; **124**: 1575–1583.
19. Sueta D, Yamamoto E, Nishihara T, Tokitsu T, Fujisue K, Oike F, Takae M, Usuku H, Takashio S, Arima Y, Suzuki S, Nakamura T, Ito M, Kanazawa H, Sakamoto K, Kaikita K, Tujita K. H2PEF score as a prognostic value in HFpEF

patients. *Am J Hypertens* 2019; **32**: 1082–1090.
20. Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction. *Circ Heart Fail* 2014; **7**: 367–377.
21. Gori M, Iacovoni A, Senni M. Haemodynamics of heart failure with preserved ejection fraction: a clinical perspective. *Card Fail Rev* 2016; **2**: 102–105.
22. Melenovsky V, Hwang S, Lin G, Redfield M, Borlaug B. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J* 2014; **35**: 3452–3462.
23. Grasso C, Capodanno D, Scandura S, Cannata S, Imme S, Mangiafico S, Pistritto A, Ministeri M, Barbanti M, Caggegi A, Chiaranda M, Dipasqua F, Giaquinta S, Occhipinti M, Ussia G, Tamburino C. One- and twelve-month safety and efficacy outcomes of patients undergoing edge-to-edge percutaneous mitral valve repair (from the GRASP Registry). *Am J Cardiol* 2013; **111**: 1482–1487.
24. Tay E, Muda N, Yap J, Muller D, Santoso T, Walters D, Liu X, Yamen E, Jansz P, Yip J, Zambahari R, Passage J, Ding Z, Wang J, Scalia G, Soesanto A, Yeo K. The MitraClip Asia-Pacific registry: differences in outcomes between functional and degenerative mitral regurgitation. *Catheter Cardiovasc Interv* 2016; **87**: E275–E281.
25. Seeger J, Müller P, Gonska B, Scharnbeck D, Markovic S, Walcher D, Rottbauer W, Wöhrle J. Percutaneous mitral valve repair in primary compared with secondary mitral valve regurgitation using the Mitral Valve Academic Research Consortium criteria. *J Invasive Cardiol* 2017; **29**: 145–150.
26. Parolari A, Pesce L, Trezzi M, Cavallotti L, Kassem S, Loardi C, Pacini D, Tremoli E, Alamanni F. EuroSCORE performance in valve surgery: a meta-analysis. *Ann Thorac Surg* 2010; **89**: 787–793 e1–2.
27. Kuwaki K, Inaba H, Yamamoto T, Dohi S, Matsumura T, Morita T, Amano A. Performance of the EuroSCORE II and the Society of Thoracic Surgeons Score in patients undergoing aortic valve replacement for aortic stenosis. *J Cardiovasc Surg (Torino)* 2015; **56**: 455–462.
28. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019; **381**: 1609–1620.
29. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Östergren J. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003; **362**: 777–781.
30. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 2014; **370**: 1383–1392.