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Initial experience with percutaneous mitral valve repair in patients with cardiac amyloidosis

Martin J. Volz[1] | **Sven T. Pleger**[1] | **Andreas Weber**[1] | **Nicolas A. Geis**[1] | **Sonja Hamed**[1] | **Derliz Mereles**[1] | **Ute Hegenbart**[2] | **Hugo A. Katus**[1,3] | **Norbert Frey**[1,3] | **Philip W. Raake**[1,3] | **Michael M. Kreusser**[1,3]

[1]Division of Cardiology, Department of Internal Medicine III, University of Heidelberg, Heidelberg, Germany

[2]Division of Hematology and Oncology, Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany

[3]DZHK (German Center for Cardiovascular Research), partner site Heidelberg/Mannheim, Heidelberg, Germany

Correspondence
Michael M. Kreusser, Department of Internal Medicine III, Division of Cardiology, Im Neuenheimer Feld 410, University of Heidelberg, 69120 Heidelberg, Germany.
Email: Michael.kreusser@med.uni-heidelberg.de

Abstract

Background: Percutaneous mitral valve repair (PMVR) is a therapeutic option for severe mitral regurgitation (MR) in patients with heart failure due to differential aetiologies. However, only little is known about the safety and efficacy of this procedure in patients with amyloid cardiomyopathy.

Methods: Five patients with cardiac amyloidosis and moderate to severe or severe MR undergoing PMVR were analysed retrospectively and compared to seven patients with cardiac amyloidosis and severe MR without intervention. Clinical and functional data, renal function and cardiac biomarkers as well as established risk scores for cardiac amyloidosis were assessed. Primary endpoint was the reduction in MR one year after PMVR. Secondary endpoints were safety, overall mortality after 12 months compared with the control group, as well as changes in clinical and functional parameters.

Results: Amyloidosis risk assessment documented amyloid cardiomyopathy at an advanced stage in all patients. Procedural, technical and device success of PMVR were all 100% and residual MR remained mild to moderate at 12 months follow-up ($P = .038$ vs before PMVR). Differences in survival compared with the control (no PMVR) group pointed to a possible survival benefit in the PMVR group ($P = .02$).

Conclusion: PMVR is a feasible and safe procedure in patients with cardiac amyloidosis and might carry a possible survival benefit in this patient group.

KEYWORDS

amyloid cardiomyopathy, cardiac amyloidosis, mitral regurgitation, percutaneous mitral valve repair

1 | BACKGROUND

The term 'amyloidosis' encompasses a group of rare diseases characterized by extracellular deposition of pathological insoluble beta-fibrillar proteins in different organs.[1] When the heart is affected by amyloid it causes progressive biventricular failure with impaired filling, but typically preserved systolic function, representing a severe form of restrictive cardiac myopathy.[2,3] The most frequent cardiac amyloidosis forms are light chain (AL) and transthyretin (ATTR) amyloidosis.[4] Although cardiac amyloidosis is rare, it has high clinical relevance due to common cardiac involvement presenting with severe heart failure and high morbidity as well as often a fatal course.[4-6] Mild mitral regurgitation (MR) in cardiac amyloidosis is a common finding.[7] Although severe MR in this patient group is rather seldom,[8] an increase in the incidence of significant MR in amyloidosis patients can be expected because of an increasing awareness for amyloid cardiomyopathy at last.[3,9] As heart failure is often severely symptomatic in these patients and largely resistant to general heart failure medication,[10] significant MR could be a treatment target to improve functional and clinical outcomes. However, operative mitral valve replacement in cardiac amyloidosis has been only reported in one case,[11] possibly because perioperative risk in this patient group undergoing mitral valve replacement has not yet been evaluated and a high mortality for cardiac surgery may be expected. Percutaneous mitral valve repair (PMVR) via MitraClip (Abbott Vascular) as well as the recently introduced Pascal (Edwards Life Science) has emerged as therapeutic options for patients with severe MR and high and/or prohibitive operative risk due to heart failure, and this has been in particular demonstrated for ischaemic and dilated cardiomyopathy.[12-14] But, only little is known about the safety and effectiveness of PMVR in patients with cardiac amyloidosis. One case report demonstrated the feasibility of the procedure in a patient with diagnosed cardiac AL amyloidosis with severe MR due to a ruptured mitral chord.[15] Due to the rising awareness of cardiac amyloidosis, an increasing number of patients with severe MR can be expected in the years to come.[16] Therefore, therapeutic option as such as PMVR in this patient group will become more relevant. The aim of this study was to investigate the safety and outcome of patients with cardiac amyloidosis treated with PMVR in our centre and compare survival to patients with severe MR and cardiac amyloidosis with a conservative treatment.

2 | METHODS

The study conforms with the principles outlined in the *Declaration of Helsinki*.[17] The study was performed in a retrospective approach. Written informed consent was obtained from all patients before PMVR allowing the clinical and scientific use of data. Data were extracted from electronic and nonelectronic medical records. The medical decision for PMVR was provided by cardiologists and cardiac surgeons in the heart team.[18] Recent reviews and several case reports give attention to the high perioperative risk of amyloidosis patients undergoing cardiac surgery or other general surgery.[19-22] Due to the severe restricted cardiomyopathy and reported risk in the literature, the risk for surgery was estimated to be high in our patient population. Therefore, PMVR was chosen as a more feasible therapy. All patients were informed about specific risks and alternatives of PMVR therapy, as well as the options for continued medical treatment and high-risk surgical mitral valve repair and gave informed written consent to the procedure. Reporting of the study conforms to broad EQUATOR guidelines.[23]

2.1 | Patient population

More than 1200 amyloidosis patients presented at the interdisciplinary Amyloidosis Centre of the University of Heidelberg between November 2012 and May 2019. Within this time period, five patients with severe symptomatic MR and cardiac amyloidosis were treated with PMVR at our institution. Further we identified seven patients with severe symptomatic MR and cardiac amyloidosis who were not treated with PMVR. Control patients did not undergo PMVR mostly due to the advanced stage of the disease. This included, besides the cardiac deterioration, most commonly a severe kidney involvement. Both ATTR and AL amyloidosis patients were included in the present analysis. The definite diagnosis of ATTR and AL amyloidosis was made according to current recommendations.[24] For AL patients, diagnosis was made by elevated light chains in serum, positive light chain ratio for kappa or lambda light chains and immunohistochemistry or congo red positive biopsy. For ATTR patients, diagnosis was made by positive immunohistochemistry or congo red positive biopsy and no evidence of light chain elevation (Table 1). One ATTR patient did not fulfil diagnostic criteria completely. The patient refused further diagnostic assessment by cardiac biopsy or bone scintigraphy. Therefore, diagnosis was made based on typical MRI and echocardiographic findings. All five patients undergoing PMVR had a complete echocardiographic workup, renal and biomarker testing at baseline as well as at three and 12 months of follow-up. 6-Minute walk test is part of our standard of care only before and three months after PMVR. Therefore, 6-minute walk test could only be compared between three months follow-up and baseline and was not available for the control group. Baseline data as well as overall survival of the control group were collected.

TABLE 1 Confirmation of the diagnosis of cardiac amyloidosis

Patient number	Amyloidosis	Diagnostic
PMVR group		
1	ATTR	Endomyocardial biopsy with positive immunohistochemistry for ATTR, no monoclonal light chains
2	ATTR	Endomyocardial biopsy positive congo red, no monoclonal light chains
3	ATTR	Typical echocardiographic and MRI finding, carpal tunnel syndrome, no monoclonal light chains
4	ATTR	Rectum biopsy with positive immunohistochemistry for ATTR, typical echocardiographic finding, no monoclonal light chains
5	AL	Bone marrow biopsy positive congo red, kappa/lambda free light chain ratio 167
Control group		
6	ATTR	Endomyocardial biopsy with positive immunohistochemistry for ATTR, Lys70Asn mutation, no monoclonal light chains
7	ATTR	Connective tissue biopsy positive congo red, positive 99 m-Tc-DPD bone scintigraphy
8	AL	Kidney biopsy positive congo red, kappa/lambda free light chain ratio < 0.1
9	AL	Rectum biopsy with positive immunohistochemistry for AL, kappa/lambda free light chain ratio < 0.1
10	AL	Endomyocardial biopsy with positive immunohistochemistry for AL, kappa/lambda free light chain ratio < 0.1
11	AL	Kidney biopsy positive congo red, kappa/lambda free light chain ratio < 0.1
12	AL	Endomyocardial biopsy positive congo red and with positive immunohistochemistry for AL, kappa/lambda free light chain ratio 58

Note: Abbreviations: AL, light chain amyloidosis; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; MRI, Magnetic Resonance Imaging, ATTR, transthyretin amyloidosis; PMVR, Percutaneous mitral valve repair.

2.2 | Pre-interventional workup

Pre-interventional workup included the patient´s medical history, clinical assessment, diuretics use and determining NYHA (New York Heart Association) class as well as a 6-minute walk test, if applicable.[25] History of cardiac amyloidosis including genetic findings, prior treatment and subtype was collected. Further, laboratory workup including high-sensitivity troponin T (hsTnT) (reference < 14 pg/mL; 3-50 pg/mL observational zone; >50 pg/mL elevated), N-terminal pro-brain natriuretic peptide (NT-proBNP) (reference < 125 ng/L), bilirubin (reference < 1.0 mg/dL) and serum creatinine (reference 0.6-1.3 mg/dL), was done in all patients. Glomerular filtration rate was calculated by using the Modification of Diet in Renal Disease formula.

2.3 | Risk assessment

To further classify the clinical presentation of the patients, established risk scores for cardiac amyloidosis as well as risk scores estimating procedural/surgical risk were calculated. Amyloidosis-specific scores included (a) the Mayo staging system for cardiac amyloidosis,[26] that gives risk points for increased hsTnT (≥35 ng/L) and NT-proBNP (≥332 ng/L) resulting in three stages (stage I: no risk point; stage II: one risk point; stage III: two risk points), (b) the revised staging Mayo staging system,[6] giving an additional risk point for NT-proBNP > 8500 ng/L resulting in four stages (stages I-IV), (c), the staging system for ATTR amyloidosis published by Gilmore et al,[27] distributing risk points for elevated NT-proBNP (> 3000 ng/L) and impaired renal function (glomerular filtration rate < 45 mL/min) resulting in three stages

(stage I: no risk point; stage II: one risk point; stage III: two risk points) as well as (d) the staging system for AL amyloidosis published by Kumar and colleagues,[28] that gives risk points for high cardiac troponin T (≥25 ng/L), NT-proBNP (≥1800 ng/L) and another additional risk point for elevated serum free kappa or lambda light chains (≥180 mg/L), resulting in four stages I–IV (stage IV: three risk points). Further, we exerted our recently published HeiRisk staging system for cardiac amyloidosis which integrates QRS duration, hsTnT and NT-proBNP for ATTR amyloidosis and hsTnT and systolic pulmonary artery (PA) pressure for AL amyloidosis.[29] As a routine for PMVR, periprocedural risk was estimated using (a) the Society of Thoracic Surgery risk score,[30] (b) the logistic euroSCORE[31] as well as I (c) the euroSCORE II.[32] Global longitudinal strain was assessed prior to every intervention as a prognostic echocardiography parameter for cardiac amyloidosis.[33]

2.4 | PMVR procedure

Mitral regurgitation and mitral valve morphology were determined by transthoracic and transoesophageal echocardiography (TTE and TEE), whereas MR was graded according to the American Society of Echocardiography guidelines.[34] Percutaneous mitral valve repair was performed under general anaesthesia in all five patients, monitored by a cardiac anaesthesiologist, guided by TEE and fluoroscopy in the cardiac catheterization laboratory, as described before.[35] In brief, the device was introduced via trans-septal puncture into the left atrium and advanced into the left ventricle. The device was closed to approximate the leaflets after grasping. Mitral regurgitation was then measured by colour flow Doppler jet characteristics and pulmonary vein flow patterns as well as vena contracta width. In case of a satisfactory reduction, the clip was deployed and a second clip was implanted in case of insufficient success. The Pascal device was relocated during the procedure as needed.[36] Intraprocedural anticoagulation with heparin was dosed to an activated clotting time of 250 to 300 seconds. Access site closure was achieved by applying one ProGlide SH closure device (Abbott Vascular) using the preclosure technique.[37] Patients were monitored in our intensive care, coronary care or advanced heart failure unit after the procedure (for at least 24 hours).

2.5 | Follow-up and statistics

For follow-up, all five patients undergoing PMVR were seen in our outpatient clinic at three and 12 months after PMVR to assess clinical, echocardiographic and biomarker outcome using TTE and measuring of NT-proBNP. Patients without PMVR were regularly seen to control clinical, echocardiographic and biomarker follow-up. The primary study endpoint was defined as the reduction in MR at 12 months post implantation. Secondary endpoints included overall mortality between the PMVR and control group. Technical, device and procedural success were defined according to the Mitral Valve Academic Research Consortium.[38]

For statistics, baseline characteristics between groups were compared using Mann-Whitney *U* test, while differences over time in the PMVR group was compared using Wilcoxon signed-rank test for ordinal and continuous variables. Categorical variables were compared using Fisher's exact test. *P*-values below 5% were considered statistically significant. Statistical analyses were performed using the SPSS statistical software package (SPSS Inc, IBM company) as well as using R (R Core Team, 2014) as well as the package ggplot2 (Wickham, 2009). Continuous data are expressed as median values and 25% and 75% percentile [Q1; Q3]. Categorical variables are expressed as absolute numbers and percentages.

3 | RESULTS

3.1 | Patient population

From November 2012 to the end of May 2019, five patients with cardiac amyloidosis underwent PMVR at our institution. Seven patients with severe MR suffering from cardiac amyloidosis not undergoing PMVR could be identified as a control group. Demographic and clinical characteristics of the patients are given in detail in Table 2. In the PMVR group, four patients were diagnosed with ATTR amyloidosis and one patient with AL amyloidosis. The AL patient in the PMVR group was treated with bortezomib/dexamethasone weekly for additional seven months after PMVR. After chemotherapy, a complete remission could be achieved in this patient. In the control group, two patients suffered from ATTR amyloidosis while five were diagnosed with AL amyloidosis. Differences in amyloidosis types between groups showed not be statistically significant ($P = .242$). The majority of ATTR patients in our study were treated before Tafamidis was approved for cardiac amyloidosis in the European Union in February 2020[39] and only one ATTR patient in the PMVR group was treated with 61 mg Tafamidis after PMVR. All control patients diagnosed with AL amyloidosis were treated with bortezomib and dexamethasone or melphalan.[40]

3.2 | Pre-procedural risk assessment using established risk scores

All patients were highly symptomatic with a median NYHA class of 3 [3; 3] in the PMVR group and 3.0 [2.0; 3.0] in the control group, respectively, pointing to overall severe heart

TABLE 2 Patient characteristics and biomarkers at baseline

Variable	PMVR	Control	*P*-value
Age (y)	74 [72; 76]	77 [68; 80]	.370
Male sex	4/5 (80%)	5/7 (71%)	1.000
NYHA (1-4)	3.0 [3.0; 3.0]	3.0 [2.0; 3.0]	.380
Device therapy			
Pacemaker	1/5 (20%)	3/7 (43%)	.576
ICD	0	0	
CRT-D	0	0	
CAD			
No CAD	1/5 (20%)	4/7 (57%)	.167
CAD not significant	2/5 (40%)	2/7 (29%)	1.000
CAD significant	2/5 (40%)	1/7 (14%)	.523
Atrial fibrillation			
No AF	2/5 (40%)	3/7 (43%)	1.000
Paroxysma AF	2/5 (40%)	0	1.000
Permanent AF	1/5 (20%)	0	.417
Comorbidities			
Hypertension	2/5 (40%)	2/7 (29%)	1.000
Hyperlipidemia	3/5 (60%)	1/7 (14%)	.222
Diabetes mellitus	1/5 (20%)	0	.417
Stroke	0	1/7 (14%)	1.000
COPD	0	1/7 (14%)	1.000
Malignant disease	0	1/7 (14%)	1.000
Biomarkers			
GFR (mL/min)	82 [77; 88]	27.9 [21; 29]	**.003**
HsTnT (pg/mL) (<14 pg/mL)	47 [39; 49]	125 [82; 319]	**.003**
Bilirubin (mg/dL) (<1 mg/dL)	0.55 [0.5; 0.8]	0.70 [0.6; 0.8]	.632
NT-proBNP (ng/L) (<125 ng/L)	2928 [2070; 7245]	17 365 [14854; 19638]	**.005**

Note: Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive lung disease; CRT-D, cardiac resynchronization therapy with defibrillator; GFR, glomerular filtration rate; hsTnT, high-sensitivity troponin T; ICD, implantable cardioverter defibrillator; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association classification of heart failure; PMVR, percutaneous mitral valve repair; values are given as median and 25% and 75% quartile or as absolute number and per cent; *P*-values are the results of a Mann-Whitney *U* test, or Fishers exact test if needed, between PMVR and control group; values < 5% were considered statistically significant.

failure in the patient cohort. To further objectify this, general operative risk scores as well as amyloidosis-specific scores were calculated (Table 3). In the PMVR group, median logistic euroSCORE was 9.8%, median euroSCORE II was 3.4% and median Society of Thoracic Surgery score was 1.7%, suggesting only mildly elevated surgical/periprocedural risk compared other patient populations prior to PMVR.[12,41,42] In contrast to this, thoracic surgery risk scores showed to be more elevated in the control group. While median logistic euroSCORE was 12.9% [7.4; 16.2], median euroSCORE II was 5.1% [4.3; 6.6] and Society of Thoracic Surgery score even revealed to be statistically significantly elevated when compared to PMVR group (4.0% [3.4; 5.0], $P = .005$). However, when again compared to published PMVR cohorts,[12,41,42] procedural risk would have been calculated lower in this amyloidosis cohort.

A different picture with regard to the medical condition of the patients turned up when amyloidosis-specific scores were used: when the Mayo score was applied, all but one patient (80%) in the PMVR group were classified as to be the highest risk group (stage III), and in the control group even all seven patients were classified in stage III. In the revised Mayo staging system, where an additional risk point is given for NT-proBNP > 8500 ng/L, only the (AL) patient undergoing PMVR met this criterion and therefore reached stage IV. All but one patient not treated with PMVR were categorized in stage IV. This difference between groups also reached statistically significance ($P = .033$). In the HeiRisk staging system,[29] three patients in the PMVR group were in the moderate risk group (60%) and two patients (40%) in the high-risk group. All seven control patients fell into the high-risk group ($P = .031$). When amyloidosis-subtype specific scores were applied, we found two ATTR patients (50%) classified as stage II and two as stage III in the staging system by Gilmore et al[27] in the PMVR group, while both ATTR patients in the control group were categorized as stage III ($P = .090$). For the AL-specific staging system that includes immunoglobin light chains, the single AL amyloidosis patient undergoing PMVR and 4 out of 5 patients not receiving PMVR were in the highest risk group IV ($P = 1.000$).[6,26,28] In summary, control patients revealed to have a rather more advanced disease compared with the PMVR group, represented by almost all risk scores applied. However, also the PMVR patients were at advanced stages of amyloid disease according to the amyloidosis scores, in contrast to what was expected from the operative risk scores.

3.3 | Pre-procedural cardiac assessment prior to PMVR

Careful assessment of standard echocardiographic parameters was performed in all patients (Table 4). Left ventricular ejection fraction (LVEF) was mild- to moderately reduced in PMVR and control group (40.0% [35; 50], 35.0% [30.0; 41.0], respectively), right atrial (RA) pressure was above normal (15 [13.8; 16.3], 20.0%[15.0; 20.0]) as well as PA pressure (42.0 [40; 45], 50.0 [46.6; 55.5]) whereas the left atrium was enlarged (50.0 [49.3; 51.0], 50.0 [44.5; 54.5]). Median left ventricular end-diastolic diameter (LVEDD) was

TABLE 3 Pre-procedural risk assessment

Variable	PMVR	Contro	*P*-value
Thoracic surgery risk scores			
STS score (%)	1.7 [1.4; 2.0]	4.0 [3.4; 5.0]	**.005**
Logistic euroSCORE (%)	9.8 [2.8; 12.0]	12.9 [7.4; 16.2]	.431
euroSCORE II (%)	3.4 [2.0; 8.8]	5.1 [4.3; 6.6]	.760
Cardiac amyloidosis risk scores			
Mayo staging system (1-3)	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	.311
Revised Mayo staging system (1-4)	3.0 [2.5; 3.0]	4.0 [4.0; 4.0]	**.033**
HeiRisk Score (1-2)	1.0 [1.0; 2.0]	2.0 [2.0; 2.0]	**.031**
Gilmore staging system for ATTR Amyloidosis (1-3)	1.5 [1.0; 2.0]	3.0 [3.0; 3.0]	.090
Kumar staging system for AL Amyloidosis (1-4)	4.0	4.0 [4.0; 4.0]	1.000

Note: Abbreviations: PMVR, percutaneous mitral valve repair; ATTR, transthyretin amyloidosis; AL, light chain amyloidosis; the Mayo staging system stratifies patients by giving risk points for elevated cardiac troponin T (≥35 ng/L) and N-terminal pro-brain natriuretic peptide (NT-proBNP) (≥332 ng/L) resulting in three stages, an additional point when NT-proBNP further increased to ≥8500 ng/L in the revised Mayo staging system, resulting in four stages; The Hei Risk Score stratifies AL patients as 'high risk' if both high-sensitivity troponin T (>58.5 pg/mL) and mean pulmonary artery pressure (>22.5 mm Hg) are elevated, resulting in two stages and stratifies ATTR patients defining 'high risk' when at least two of the following criteria are met: prolonged QRS duration (>104 ms ng), elevated NT proBNP (>6330 ng/L) or elevated high-sensitivity troponin T > 55 pg/mL, resulting in two stages; the Gilmore staging system stratifies ATTR patients by giving risk points for high NT-proBNP (≥3000 ng/L) and for low glomerular filtration rate (<45 mL/min), resulting in three stages; an extended Mayo staging for AL Amyloidosis published by Kumar et al. stratifies AL patients by giving risk points for high cardiac troponin T (≥25 ng/L), N-terminal pro-brain natriuretic peptide (≥1800 ng/L) and another additional risk point for elevated serum free kappa or lambda light chains (≥180 mg/L), resulting in four stages; values are given as median and 25% and 75% quartile or as absolute number and per cent; *P*-values are the results of a Mann-Whitney *U* test, between PMVR and control group; values <5% were considered statistically significant.

in a normal range (<55 mm) in both groups, reflecting the restrictive nature of cardiomyopathy in this patient group (51.5 [44.0; 61.25]; 45.0 [38.0; 48.0]). One patient in the PMVR group had a mixed form of dilated cardiomyopathy and amyloidosis with functional MR due to a left ventricular dilatation (LVEDD 71mm). Therefore, median LVEDD was numerical higher in the PVMR group. However, this difference did not reach statistical significance. Left ventricular (LV) longitudinal function was highly reduced in both groups measured by longitudinal strain (10.9 [8.6; 11.7], 7.7 [5.9; 9.3]). Further, right ventricular (RV) function was highly decreased as shown by reduced longitudinal right ventricular shortening (tricuspid annular plane systolic excursion (TAPSE) of 1.1 cm [1.0; 1.5] in the PMVR group, 1.2 [1.0; 1.3] in the control group). There were no statistically significant differences between groups regarding echocardiographic parameters. In contrast, renal functioning revealed a relevant difference between groups: for patients undergoing PMVR, median glomerular filtration rate showed to be 82 mL/min [77; 88] measured by the Modification of Diet in Renal Disease formula, while control patients had a median glomerular filtration rate of 28 mL/min [21; 29] ($P = .003$). Cardiac biomarkers, measured by hsTnT as well as NT-proBNP also reflected the different stages of disease between groups. In the PMVR group, high-sensitivity troponin T was elevated with a median of 47 pg/mL [39; 49] as well as NT-proBNP (2928 ng/L [2070; 7245]). Even though this represents severe heart failure in these patients, biomarkers were significantly more elevated in control patients (Table 2). Elevated NT-proBNP in the control group must be interpreted as a sign of the further advanced stage of disease in this group but also a result of the impaired kidney function.

3.4 | Procedural data

Aetiology of severe MR in patients undergoing PMVR was dilatation of the annulus alone in one case, leaflet restriction in two cases, leaflet prolapse in one case and the combination of dilatation and restriction in one case. Most patients in the control group presented with severe leaflet restriction or tethering (Table 5). In all PMVR patients, the deployment of the clip was successful (technical success 100%). No device-related complications were observed. Implanted devices

TABLE 4 Baseline Echocardiography data

Variable	PMVR	Control	*P*-value
LA diameter (mm)	50.0 [49.3; 51.0]	50.0 [44.5; 54.5]	.924
LVESD (mm)	41.0 [31.5; 53.8]	35.0 [32.0; 43.0]	.597
LVEDD (mm)	51.5 [44.0; 61.25]	45.0 [38.0; 48.0]	.255
EF (%)	40.0 [35.0; 50.0]	35.0 [30.0; 41.0]	.512
Longitudinal Strain (-%)	10.9 [8.6; 11.7]	7.7 [5.9; 9.3]	.889
TAPSE (cm)	1.1 [1.0; 1.5]	1.2 [1.0; 1.3]	.924
RV diameter (mm)	35.5 [28.3; 42.3]	39.0 [34.5; 45.0]	.636
RA pressure (mmHg)	15.0 [13.8; 16.3]	20.0 [15.0; 20.0]	.371
Systolic PA pressure (mmHg)	42.0 [40; 45]	50.0 [46.5; 55.5]	.090
VCI contractility	yes 2/5 (40%)	yes 0/7	.152
VCI diameter (mm)	24.5 [23.3; 25.5]	26.0 [24.0; 27.0]	.633
TR (1-3)	1.0 [0.8; 1.3]	2.0 [1.0; 2.0]	.222
MR (1-3)	3.0 [3.0; 3.0]	3.0 [3.0; 3.0]	1.000

Note: Abbreviations: EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral valve regurgitation; PMVR, percutaneous mitral valve repair; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation; VCI, vena cava inferior; values are given as median, 25% and 75% quartile or as absolute number and per cent; *P*-values are the results of a Mann-Whitney *U* test, or Fishers exact test if needed, between PMVR and control group; values < 5% were considered statistically significant.

TABLE 5 Procedural data

Variable	PMVR	Control	*P*-value
Aetiology of MR			
Anulus dilatation	1/5 (20%)	1/7 (14%)	1.000
Leaflet restriction/ tethering	2/5 (40%)	5/7 (71%)	.417
Anulus dilatation + leaflet restriction	1/5 (20%)	0	.559
Leaflet prolapse	1/5 (20%)	0	.360
Leaflet prolapse and ruptured cord	0	1/7 (14%)	1.000
Technical success	5/5 (100%)		
Device success	5/5 (100%)		
Procedural success	5/5 (100%)		
MR post implantation	1.0 [1.0; 1.0]		
Procedure time (min)	89 [89; 95]		
Radiation time (min)	9.3 [9.1; 9.3]		

Note: Abbreviations: device success = effectiveness of the device in reducing the severity of MR to a trace level; MR, mitral valve regurgitation; PMVR, percutaneous mitral valve repair; procedural success = absence of major device or procedure-related serious adverse events; Technical- device- and procedural success according to MVARC (Mitral Valve Academic Research Consortium) (38). Technical success, ability of the device to be deployed as intended and the delivery system successfully retrieved without procedural mortality or need for emergency surgery or intervention; values are given as median and 25% and 75% quartile or as absolute number and per cent; *P*-values are the results of Fishers exact test between PMVR and control group.

were MitraClip (Abbott Vascular) in four patients and Pascal (Edwards Life Science) in one patient. In one patient, two MitraClip devices were inserted, whereas all other patients received one device. Device and procedural success were both 100% according to the Mitral Valve Academic Research Consortium.[38] Median procedure and radiation time were lower compared with other studies investigating PMVR in other patient groups.[12] Procedural data are given in detail in Table 5.

3.5 | Outcome after three and 12 months

All five patients undergoing PMVR survived the one-year follow-up period. Mitral valve regurgitation could be successfully reduced to mild in three patients and to moderate in two patients after 12 months follow-up. This persistent reduction in MR was statistically significant ($P = .038$), even in the small number of patients. However, when echocardiography parameters were followed over the one-year period, no significant improvements were seen (Table 6). This is in particular remarkable for longitudinal strain, TAPSE, RV diameter and systolic PA pressure, all parameters that have been seen to improve in PMVR cohorts with other aetiologies of the underlying cardiac disease.[43-46] Also, systolic blood pressure which has been highlighted as an important parameter of prognosis in cardiac amyloidosis,[6] did not change 12 months after PMVR (110mm Hg [100; 110]. vs 100mm Hg [100; 140]). 6-minute walk test showed no significant improvement three months after PMVR (386 m [338; 421]) when compared to baseline (335 m [205; 376,5]). In accordance with this lack of functional improvement, cardiac biomarkers as hsTnT (47pg/mL [39;49] vs 49pg/mL [24; 55]) and NT-proBNP (2928 ng/L [2070; 7245], vs 6311 [5310; 6804]) and renal function as well as serum bilirubin did not significantly change/improve over the 12 months period. Further, PMVR in cardiac amyloidosis patients did not result in a significant

TABLE 6 Echocardiography data at follow-up after PMVR

Variable	Baseline	3 mo	12 mo	*P*-value
LA diameter (mm)	50.0 [49.3; 51.0]	49.5 [46.8; 52.3]	53.0 [49.0; 55.0]	.450
LVESD (mm)	41.0 [31.5; 53.8]	39.5 [33.8; 44.8]	36.5 [36.0; 50.0]	.655
LVEDD (mm)	51.5 [44.0; 61.25]	50.0 [47.0; 53.8]	47.5 [44.0; 62.0]	.068
EF (%)	40.0 [35.0; 50.0]	42.5 [38.3; 47.5]	45.0 [24.0; 50.0]	.109
Longitudinal Strain (-%)	10.9 [8.6; 11.7]	8.5 [6.9; 10.3]	7.0 [5.5; 11.3]	.080
TAPSE (cm)	1.1 [1.0; 1.5]	1.8 [1.5; 2.0]	1.3 [1.2; 1.5]	.593
RV diameter (mm)	35.5 [28.3; 42.3]	33.0 [32.0; 41.2]	38.5 [38.0; 45.0]	.066
RA pressure (mm Hg)	15.0 [13.8; 16.3]	10.0 [5.0; 15.0]	15.0 [10.0; 20.0]	.157
Systolic PA pressure (mm Hg)	42.0 [40; 45]	37.0[29; 44]	37.5 [34; 41]	.564
VCI contractility	yes 2/5 (40%)	yes 2/4 (50%)	yes 2/5 (40%)	1.000
VCI diameter (mm)	24.5 [23.3; 25.5]	21.0 [18.0; 23.5]	27.5 [21.0; 30.0]	.180
TR (1-3)	1.0 [0.8; 1.3]	0.5 [0.0; 1.3]	1.0 [0.0; 2.0]	.564
MR (1-3)	3.0 [3.0; 3.0]	1.0 [1.0; 1.0]	1.0 [1.0; 2.0]	**.038**

Note: Abbreviations: EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral valve regurgitation; PMVR, percutaneous mitral valve repair; RA, right atrium; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation; VCI, vena cava inferior; *P*-values are the results of a Wilcoxon signed-rank test comparing baseline and 12 mo follow-up; values < 5% were considered statistically significant; values are given as median, 25% and 75% quartile or as absolute number and per cent.

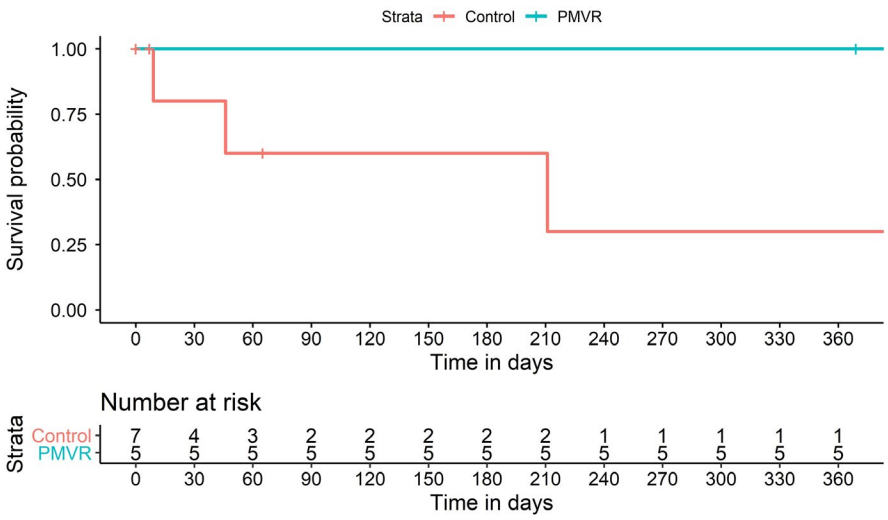

FIGURE 1 Overall survival at 12 mo between PMVR group and control group. Kaplan-Meier survival curve for PMVR and control group, vertical bars represent censored events, *P*-value is the result of a log rank test comparing overall survival between groups. PMVR, percutaneous mitral valve repair

functional improvement in terms of a reduction of NYHA class or torasemide intake. However, patients undergoing PMVR showed to have a significant better overall survival compared with the control group ($P = .006$). Three out of seven patients in the control group did not survive the 1-year follow-up period (Figure 1).

4 | DISCUSSION

Novel therapeutic concepts for patients with amyloid cardiomyopathy are urgently needed, as a substantial increase in the diagnosis of amyloid cardiomyopathy in the years to come can be expected.[3,9] We here report our experience of

five patients with cardiac amyloidosis and significant MR undergoing PMVR. Whereas recently, Scully and colleagues reported on patients with cardiac amyloidosis and transcatheter aortic valve implantation,[47] the present data represent the largest set of amyloidosis patients investigated regarding interventional atrio-ventricular valve repair and it is the first study to demonstrate a significant reduction of MR in these patients and to compare survival to a control group over a 12 months follow-up period.

4.1 | PMVR in specific cardiomyopathies

Whereas primarily, the MitraClip device was intended for patients with degenerative MR,[48] functional MR due to ischaemic and nonischaemic cardiomyopathies was treatment target in the recent MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trials.[12,42] In both studies for functional MR, the majority (about 60%) of patients had ischaemic cardiomyopathy, whereas the remaining patients were not itemized in detail for the type of cardiomyopathy ('non-ischemic'). However, in the clinical situation, the question whether the underlying type of cardiomyopathy may affect the PMVR result is of relevance. In this regard, a multicentre retrospective study could demonstrate a significant reduction of MR, NYHA functional class as well as an improvement in the functional capacity after PMVR in patients with dilated cardiomyopathy,[49] and dilated cardiomyopathy patients had similar results regarding technical success, clinical outcome and mortality when compared to patients with ischaemic cardiomyopathy.[14] Likewise, in patients diagnosed with hypertrophic obstructive cardiomyopathy, a significant reduction in systolic anterior movement and pressure gradients using PMVR has been shown,[50] leading to a clinical benefit in this patient group when PMVR is applied.[51] But, other distinct cardiomyopathies have not been specifically evaluated regarding PMVR, and data illuminating this aspect are warranted to facilitate therapeutic decisions in patients with functional MR. Therefore, according to current knowledge, a significant difference between devices regarding outcome is unlikely or still needs to be demonstrated.

4.2 | Technical aspects of PMVR in amyloidosis patients

In amyloidosis patients, reported aetiologies of severe MR are local amyloid infiltration and ruptured cordae.[7,11,52] As a pathophysiological mechanism, a reduced elasticity of the mitral valve in these patients was demonstrated.[53] However, only little is known about the pathophysiology of MR in amyloidosis and treatment strategies are not defined: For instance, data on surgical mitral valve repair is—except one report[11]—not available, possibly because the operative risk is rated as too high for surgical treatment. Likewise, the decision for PMVR over an operative approach was made in our patients due to the high intraoperative risk secondary to restrictive heart failure as well as the overall limited prognosis in this patient group. One single case report by Krishnaswamy and colleagues discussed potential technical challenges of PMVR due to cardiac amyloidosis: Leaflet thickening, a substantial flail gap between the leaflets, and chordal shortening as well as possible post-procedural mitral stenosis due to leaflet thickening.[15] Although these pitfalls, all five procedures presented in the present study could be completed with technical success and without device dysfunction. It can be argued that two patients developed recurrent, moderate MR twelve months after the intervention and therefore only reached a partial success. However, a reduction from severe to moderate can still be seen as relevant improvement.[54] Therefore, our data demonstrate that PMVR is a safe procedure in this patient group with a good and lasting outcome for MR and little risk for post-procedural stenosis.[55] The use of different PMVR systems (MitraClip and Pascal) is an issue that needs to be discussed. However, head to head comparison between both devices are still absent and recent data suggest good efficacy, safety and feasibility of the newly introduced Pascal system.[56] Therefore, according to current knowledge, a significant difference between devices regarding outcome is unlikely or still needs to be demonstrated.

4.3 | Clinical benefit from PMVR

Despite technical success, a clinical improvement after PMVR could not be demonstrated in our study, in very contrast to the well-described functional improvements after PMVR in other clinical settings.[13,57] New York Heart Association functional class as well as the 6-minute walk test did not improve post-procedural in our patients. Moreover, NT-proBNP and hsTnT levels as markers of heart failure in general and valuable prognostic markers specifically for amyloidosis[6,26-29] did not decline after the procedure over time. A possible explanation for this may be the progressive character of amyloid cardiomyopathy: One-year mortality in cardiac amyloidosis can be estimated to be about 30%[26,29] and even higher in patients with advanced heart failure,[58] documenting a rapid deterioration in patients with amyloid cardiomyopathy. Three out of seven patients in our control group with conservative treatment of MR did not survive the 12 months follow-up, demonstrating that functional MR may be an additional risk factor and/or sign of a particular advanced disease in amyloidosis patients. Allowedly, our

control and PMVR groups are difficult to compare, and a more advanced disease in the conservative group can be assumed from our data and also due to the clinical selection process for PMVR. N-terminal prohormone of brain natriuretic peptide was much higher in the control group which can be seen as a sign of a further advanced stage of disease in this group as well as a result of the also impaired kidney function. This also reflects the fact that patients with a far advanced stage of the disease were not further considered for an interventional therapy of MR, making an extrapolation of our comparison to larger populations for both groups, PMVR and control, rather difficult. However, from our view, it was highly unexpected that one-year survival was 100% in the PMVR group. Especially considering the highly elevated amyloidosis risk scores and cardiac biomarkers in this group.

But how can expected survival be calculated in such a patient cohort? When stratified by Society of Thoracic Surgery or logistic euroSCORE,[59,60] the five patients in the PMVR group appear to have a rather low pre-procedural risk compared with nonamyloidosis patients undergoing PMVR. Yet, patients with heart failure due to cardiac amyloidosis represent a unique patient population in which a patient-tailored risk assessment is indispensable.[29] Based on established risk stratification systems for amyloidosis,[6,26-29] for the four ATTR patients in the PMVR group, the median survival would be estimated to be less than 12 months [26] and even less than six months for the one AL patient.[28] In contrast to this poor prognosis, all five patients survived the 12 months follow-up period without cardiac decompensation which could point to a possible benefit from the mitral valve intervention. Further, no relevant clinical disease progression was observed in this group, measured by any clinical, functional or biomarker outcome. When compared to the even more advanced amyloid disease in the control group, our data may also add to the idea of importance of the right timing for PMVR in cardiac amyloidosis, as already described for other patient cohorts.[61] Considering PMVR in cardiac amyloidosis especially at an early stage could therefore be a feasible treatment option.

4.4 | Heart failure due to amyloid cardiomyopathy

When looked at from a heart failures specialist´s view, therapeutic options for cardiac amyloidosis are very limited: While standard heart failure medication is ineffective, medical therapy is often restricted to diuretics for symptom relief.[62] Whereas AL amyloidosis can be treated in the hands of an adept haematologist,[63] and novel treatment options emerged for cardiac amyloidosis in recent years,[64] this therapeutic armament is effective only in early stages of amyloid cardiomyopathy, but not in advanced stages of the disease.[40,64] When terminal heart failure due to amyloidosis is present, heart transplantation may be a viable treatment in selected patients and few experienced centres.[65,66] However, mortality on transplant waiting lists are excessively high in amyloidosis patients,[58] and strategies to bridge those critical patients are urgently needed. We and others have demonstrated that PMVR is an option as 'bridge to transplant' in nonamyloid cardiomyopathy patients awaiting heart transplantation.[67] Although the majority of patients in the present study were too aged for a 'bridge to transplant' approach, our data may add to the idea that interventional treatment of MR may significantly extend the therapeutic possibilities for those critical ill patients.

4.5 | Limitations

This study was conducted as a single centre, retrospective study containing only a small number of patients. Therefore, concerns about the safety of the procedure cannot be completely removed. Patients included did not fulfil established criteria for PMVR reflected by risk scores like the Society of Thoracic Surgery score or logistic euroSCORE. However, it can be argued that our patients undergoing PMVR can be assessed at least medium risk using established scoring systems for cardiac amyloidosis. Amyloidosis type (AL or ATTR) was not equally distributed between groups, and the prognosis for AL patients is known to be inferior to ATTR. We decided to include both, AL and ATTR patients, in this analysis because the underlying cause of heart failure is a restrictive cardiomyopathy in both entities and therefore a comparison of cardiac functioning seems reasonable, even in these heterogenous groups. Furthermore, we are aware that comparison between groups (PMVR and control) is biased by the differences in baseline risk, resulting from the selection process for PMVR. Due to this risk of bias and the low number of cases, a statistically evaluation of difference between groups regarding overall survival is only arguably justifiable. The low number of cases and events would not allow an adequate adjustment for possible sources of bias.

5 | CONCLUSION

Our data demonstrate that PMVR in cardiac amyloidosis patients can be considered a safe and effective procedure regarding MR reduction. The possible impact of PMVR on survival and clinical outcomes needs to be further evaluated against the background of the rapid progression of the underlying disease. For now, when severe MR develops in patients with cardiac amyloidosis, the decision for PMVR and the

timing needs to carefully considered and ideally be made in an interdisciplinary heart team.[18]

CONFLICT OF INTEREST

STP and PWR received speaker honoraria from Abbott Vascular. MMK, NAG and PWR are investigators in the RESHAPE-HF (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) study. MMK and STP received research grants from Abbott. All other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

ORCID

Michael M. Kreusser https://orcid.org/0000-0001-8938-7579

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