ORIGINAL RESEARCH ARTICLE

PASCAL-based mitral valve repair in an all-comer population: acute and mid-term clinical results

Philipp Schlegel[1,2] (ID), Patricia Crespo López[1], Michael M. Kreusser[1,2], Hugo A. Katus[1,2], Norbert Frey[1,2], Nicolas A. Geis[1]* and Philip W.J. Raake[1,2]

[1]*Department of Internal Medicine III, Cardiology, University Hospital Heidelberg, University of Heidelberg, Im Neuenheimer Feld 410, Heidelberg, 69120, Germany; and* [2]*DZHK [German Centre for Cardiovascular Research], Partner site Heidelberg/Mannheim, Heidelberg, Germany*

Abstract

Aims   We investigated short and mid-term safety and efficacy of the PASCAL system for percutaneous mitral valve repair (PMVr) in severe mitral regurgitation (MR) in an all-comer population.

Methods and results   In the first consecutive 41 patients undergoing PMVr using the PASCAL system in our centre, procedural success and safety were assessed. Efficacy in improving MR and functional class were evaluated. Median patient age was 74 years, 58.5% were male patients, and median European System for Cardiac Operative Risk Evaluation Score II was 5.1%. All patients suffered from severe MR with 59% functional MR, 29% degenerative MR, and 12% of mixed aetiology MR. The technical success rate was 90%, limited by four cases where PASCAL implantation was aborted due to a prohibitive mitral gradient. On average, 1.16 PASCAL devices per patient were implanted. All patients successfully implanted with a PASCAL device were discharged with MR grade $\leq$ 2 and 79% with MR grade $\leq$ 1. Mean follow-up was 8.7 ± 4.9 months. Ninety-seven per cent of patients remained at MR $\leq$ 2 at follow-up, which translated into a significantly improved New York Heart Association functional class as well as a significant reduction of systolic pulmonary artery pressure and brain natriuretic peptide levels. The procedure-related rate for major adverse events was 3%. Neither early nor late single-leaflet detachment was found. In one patient, air embolism occurred, resulting in modification of the PASCAL instructions for use.

Conclusions   Percutaneous mitral valve repair using PASCAL in a real-world, all-comer population was feasible and safe, resulting in a significant mid-term reduction of MR with persistent clinical improvement.

Keywords   Heart failure; Mitral valve regurgitation; Mitral valve repair; Edge-to-edge repair; Leaflet repair; PASCAL device

Introduction

Severe mitral regurgitation (MR) can result from distinct aetiologies. Primary or degenerative MR is caused by anatomical destruction of the leaflets or chordal structures, while secondary or functional MR is a consequence of left ventricular or left atrial dilation. In either case, severe MR defines a poor prognosis due to excess morbidity and mortality.[1,2] With the ageing population, prevalence of severe MR in patients with multiple comorbidities and high surgical risk is rapidly increasing.[3,4] The development of catheter-based approaches for treatment of MR and in particular the introduction of the MitraClip edge-to-edge repair system (Abbott vascular, Santa

Clara, California, USA) greatly extended therapeutic possibilities for these patients. While the anatomical inclusion criteria for the EVEREST trial[5] clearly determine suitable patients for interventional percutaneous mitral valve repair (PMVr), there remains a considerable number of patients not suitable according to these criteria. Although, in clinical routine, MitraClip devices have been successfully used in anatomies beyond the EVEREST criteria, the need for an extension of the armamentarium for PMVr persists. In February 2019, the PASCAL transcatheter mitral repair system (Edwards Lifesciences, Irvine, California, USA) received CE approval for treatment of severe MR of functional and degenerative origin. This system is also based on leaflet repair technology

but differs in device construction, steering, and grasping function. The recently published 1 year results of the CLASP trial[6] confirmed safety and significant improvement of MR and functional status in a yet strictly selected cohort. The aim of this study was to evaluate device success and safety as well as mid-term efficacy in a real-world cohort. This cohort consists of the first 41 cases of severe symptomatic MR, which were treated using the PASCAL repair system in our high-volume centre.

Methods

Patient selection

The present study was performed as retrospective observational analysis and conforms with the principles outlined in the Declaration of Helsinki. The study cohort comprises an unselected all-comer population of the first 41 patients undergoing PMVr using the PASCAL repair system in our centre. All patients were screened by transthoracic and transesophageal echocardiography prior to heart team discussion. Patients with morphological criteria[7] rendering successful PMVr unlikely or impossible were excluded except for one patient with a combined mitral valve disease non-operable due to porcelain aorta. In this case, a bailout procedure was performed. All patients were evaluated by our heart team and allocated to PMVr due to high surgical risk, frailty, or inoperability. Every patient gave informed written consent for interventional MR repair. Overall, 37 patients were successfully implanted with at least one PASCAL device and thus enrolled for follow-up.

PASCAL procedure

The PMVr procedure using the PASCAL valve repair system has been described previously.[6–8] Briefly, the PASCAL system consists of a 22F guide sheath, a steerable catheter, and the implant catheter with the pre-attached PASCAL device. The guide sheath with the steerable and implant catheter allows three-dimensional manoeuvring of the device. Unique constructional features of the PASCAL device compared with third generation MitraClip are a nitinol backbone with broader shaped paddles and a central 5 mm spacer, aimed to reduce the central MR jet. The contoured paddle design and the flexible composition intent to reduce leaflet stress. The PASCAL system also supports independent leaflet grasping, which allows optimization of leaflet insertion for anterior and posterior leaflet separately. Finally, the PASCAL implant can be fully elongated which shall improve manoeuvrability within the valve and reduce chances of chordal entanglement. All interventions were performed under general anaesthesia with transesophageal echocardiography and

fluoroscopic guidance. The femoral vein access was routinely closed using the Proglide Perclose device (Abbott Cardiovascular, Plymouth, MN, USA). Upon completion of the intervention, patients were extubated and transferred to our intermediate care unit for post-interventional observation of at least 6 h.

Grading of mitral regurgitation severity and follow-up

Mitral regurgitation severity was graded at baseline before PASCAL device implantation including transthoracic and transesophageal echocardiography as well as right heart catheterization. Follow-up was performed by transthoracic echocardiography using the integrated approach recommended by current guidelines.[9] MR quantification based on the proximal isovelocity surface area was not assessed on regular basis due to its technical limitations and comparatively high variance. MR was graded in mild (1), moderate (2), or severe (3) MR as recommended by the Mitral Valve Academic Research Consortium (MVARC).[10] Procedural endpoints for device success and major adverse events (MAE) were defined according to MVARC criteria.[11] With the first follow-up timepoint for most patients being beyond 30 days, device success was assessed at time of discharge. Data collection was performed retrospectively in accordance with our local ethics committee (S-299/2015). At baseline and follow-up cardiac biomarkers, high-sensitive troponin T (hsTNT) and NT-pro brain natriuretic peptide (NT-proBNP) were measured.

Statistical analysis

All data sets were evaluated using D'Agostino–Pearson omnibus tests and Q–Q plot for normality and accordingly expressed as mean ± standard deviation or median and interquartile range (IQR). Categorized data are presented as number of patients and percentages. For statistical analysis, Mann–Whitney U or Wilcoxon matched-pairs signed-rank test were used when appropriate. Statistical analysis was performed using GraphPad Prism 9.0 (GraphPad Software, San Diego, USA). For all statistical tests, a P value < 0.05 was accepted as statistically significant.

Results

Baseline clinical and echocardiographic characteristics

A total of 41 symptomatic patients with moderate-severe or severe MR were assigned to interventional mitral valve repair

using the PASCAL repair system between April 2019 and March 2020. The median patient age was 74 years (IQR: 63–81) and 58.5% were male patients. The median European system for Cardiac Operative Risk Evaluation Score II was 5.1% (IQR: 3–8), underlining the elevated mortality risk in this patient population. Comorbidities were frequent with arterial hypertension (81%), atrial fibrillation (66%), chronic lung disease, and coronary artery disease (each 54%) representing the most common pathologies. Eighty-eight per cent of patients presented with a limited functional New York Heart Association (NYHA) class of III or IV. In accordance with impaired functional capacity, left ventricular ejection fraction (LVEF) [38% (IQR: 20–53)] and cardiac index [2.1 L/min/m^2 (IQR: 1.8–2.4)] were found profoundly reduced. Forty-six per cent of patients had an LVEF < 35%. This is further underlined by the severely elevated NT-proBNP [4351 ng/L (IQR: 1827–12 386)]. Invasively measured systolic pulmonary arterial pressure (sPA) was elevated with a mean of 52 ± 15 mmHg. All patients suffered from severe MR with 58.5% functional MR, 29.3% degenerative MR, and 12.2% of mixed aetiology. The mean vena contracta width derived from three-chamber view was 7.1 ± 3.0 mm. Detailed clinical and echocardiographic baseline patient characteristics are summarized in *Table 1*.

Procedural outcomes

Successful interventional leaflet repair was achieved in 37 patients using the PASCAL mitral repair system. The technical success according to MVARC criteria was 90% (37/41 patients) (*Figure 1*). The rate of success was 100% (12/12 patients) for degenerative MR, 88% (21/24 patients) for functional MR, and 80% (4/5 patients) for MR of mixed aetiology. At discharge, 100% of patients undergoing successful PASCAL device implantation had an MR ≤ 2. Seventy-nine per cent of patients were discharged with an MR ≤ 1. The degree of MR was significantly reduced at discharge with a mean reduction of severity of 1.9 ± 0.6. In 76% of patients (28/37), a reduction of ≥2 MR grades was achieved (*Figure 2A*). The average number of PASCAL devices per patient was 1.16 ± 0.4. Thirty-two patients (86%; 32/37) were implanted with one PASCAL device, four patients (11%; 4/37) were implanted with two devices, while only one case (3%; 1/37) required the implantation of three PASCAL devices. The device success according to MVARC criteria was 87% (36/41 patients). Overall, four patients could not be implanted. In three cases, the PASCAL device could not be implanted due to a mean mitral valve gradient > 5 mmHg. Among these, one case was a bailout procedure due to inoperability as noted above. The other two cases presented with moderate to severe restriction of leaflet mobility. One of these patients had already undergone surgical mitral valve reconstruction. In the fourth, non-implanted patient, a severe

Table 1 Baseline clinical and echocardiographic parameters of all patients intended for PASCAL-based mitral valve repair (*n* = 41)

| Baseline patient characteristic (*n* = 41)	
Age (years) (median/IQR)	74/(63–81)
Male (*n*/%)	24/58.5
NYHA I (*n*/%)	0/0
NYHA II (*n*/%)	5/12.2
NYHA III (*n*/%)	26/63.4
NYHA IV (*n*/%)	10/24.4
NT-proBNP (ng/L) (median/IQR)	4353/(1827–12 386)
hsTNT (pg/mL) (median/IQR)	35/(20–53)
Creatinine (mg/dL) (mean ± SD)	1.34 ± 0.8
EuroSCORE log (%) (median/IQR)	14.7/(9–29)
EuroSCORE II (%) (median/IQR)	5.1/(3–8)
Comorbidities	
Arterial hypertension (*n*/%)	33/80.5
Atrial fibrillation (*n*/%)	27/65.9
Coronary artery disease (*n*/%)	22/53.7
Chronic lung disease (*n*/%)	22/53.7
Chronic renal failure	16/39.0
(Crea > 1.3 mg/dL) (*n*/%)	
Malignancy (*n*/%)	14/34.2
Diabetes mellitus (*n*/%)	13/31.7
Previous cardiac surgery (*n*/%)	5/12.2
Device therapy	
ICD (*n*/%)	11/26.8
CRT (*n*/%)	6/14.6
MR severity	
MR = 3 (*n*/%)	40/97.5
MR leading segment A2/P2 (*n*/%)	36/87.8
MR valve area (cm^2) (mean ± SD)	5.78 ± 1.56
Vena contracta (mm) (mean ± SD)	7.14 ± 2.98
MR aetiology	
Functional (*n*/%)	24/58.5
Degenerative (*n*/%)	12/29.3
Mixed (*n*/%)	5/12.2
Echocardiographic parameters	
LVEF (%) (median/IQR)	38/(20–53)
Cardiac index (L/min/m^2)	2.1/(1.8–2.4)
LVEDD (mm) (mean ± SD)	57.2 ± 10.1
LVESD (mm) (mean ± SD)	45.2 ± 13.4
MPG MV (mmHg) (mean ± SD)	1.4 ± 0.7
LA Diameter (mm) (mean ± SD)	51.8 ± 6.3
sPA (mmHg) (mean ± SD)	51.8 ± 14.6

CRT, cardiac resynchronization therapy; hsTNT, high-sensitive troponin T; ICD, implantable cardiac defibrillator; IQR, interquartile range; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MPG MV, mean pressure gradient of the mitral valve; MR, mitral regurgitation; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association functional class; sPA, systolic pulmonary arterial pressure.

MR at a mitral valve gradient close to 5 mmHg remained after leaflet capture. Thus, the procedure was aborted without PASCAL implantation. A detailed summary of mitral valve anatomy is given in Supporting Information, *Table S1*.

Functional and clinical results on follow-up

The average follow-up period was 8.7 ± 4.9 months. Of the 37 patients that had undergone PMVr using PASCAL repair system, follow-up data were available for 31 patients (84%;

Figure 1 Study flow chart. Patients were characterized regarding mitral regurgitation by transthoracic echocardiography, transesophageal echocardiography, and invasive haemodynamics. Prior to PASCAL mitral repair, all patients received individual optimized heart failure therapy as well as coronary interventions or cardiac resynchronization therapy if indicated. MR, mitral regurgitation.
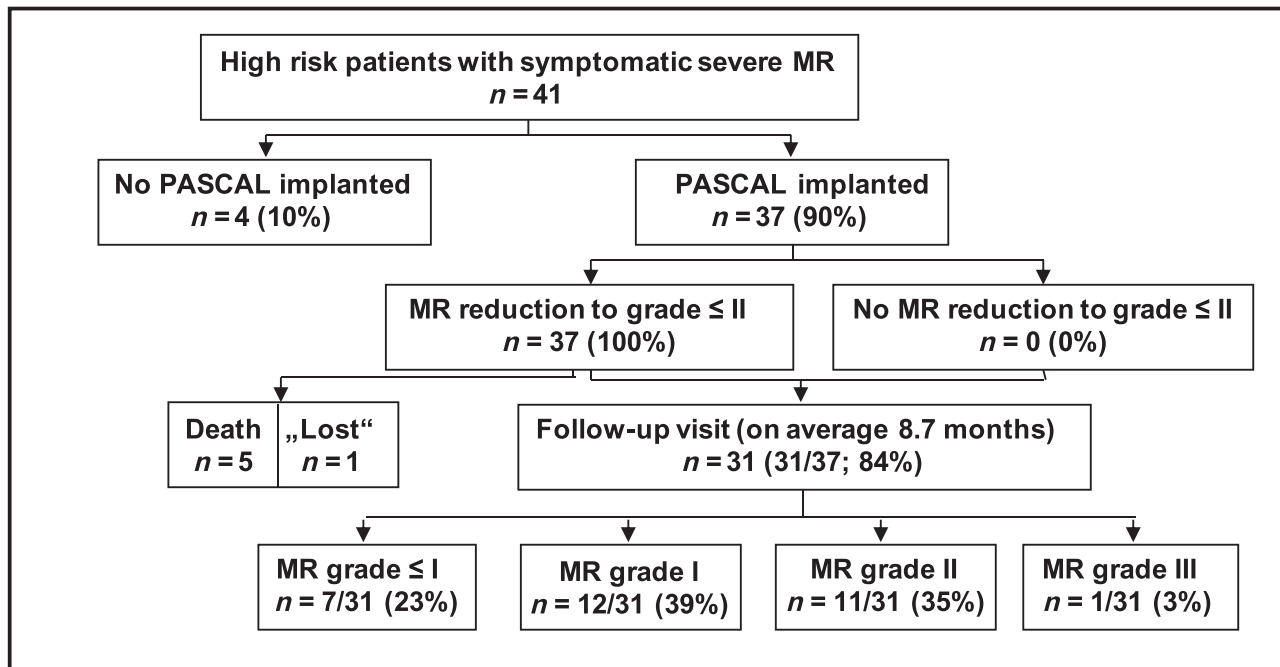
31/37). One patient (3%; 1/37) could not be recruited for follow-up visit. Five patients (13%; 5/37) died before follow-up visit (at 29, 42, 212, 215, and 231 days post procedure) (*Figure 1*). None of the deaths were directly associated with the device implantation procedure. Echocardiographic MR assessment confirmed a sustained significant reduction of MR severity at follow-up visit (*Figure 2A*). MR ≤ 1 was present in 19 patients (61%; 19/31). Thirty patients presented MR ≤ 2 (97%; 30/31). Compared with baseline values, the reduction of MR was statistically significant ($P < 0.0001$). Neither early nor late single-leaflet device attachment occurred. Successful MR repair translated not only into significantly reduced sPA (53 ± 16 vs. 43 ± 16 mmHg; $P < 0.005$) (*Figure 2E*) but also improved NYHA functional class. Seventy-three per cent of patients reported an improvement of at least one NYHA grade at the time of follow-up visit ($P < 0.0001$). Of the 31 patients, 58% (18/31) were in NYHA II class or below at follow-up visit (*Figure 2B*). Analysis of NT-proBNP and circulating hsTNT confirmed reduction of chronic cardiac stress and wall tension as both biomarkers had decreased after successful PASCAL implantation. For 23 patients, the values for hsTNT and NT-proBNP at baseline and follow-up were available for sequential analysis. While hsTNT values presented only a trend towards reduction in successfully implanted patients [baseline 24 pg/mL (IQR:

17–49) vs. follow-up 19 pg/mL (IQR: 15–34), $n = 23$], NT-proBNP values were found significantly decreased after PASCAL device implantation [baseline 3903 ng/L (IQR: 1464–6598) vs. follow-up 1587 ng/L (IQR: 725–2766); $n = 23$] (*Fig. 2C,D*). A detailed summary is given in *Table 2*.

Procedural major adverse events and major adverse events during follow-up

In the 41 patients undergoing PASCAL device implantation, total rate of acute intervention related MAE was 2.4% (1/41 patients). In this case, we observed a periinterventional air embolism, with brief haemodynamic instability and ST-segment elevation in right coronary artery corresponding leads. Immediate angiography excluded coronary occlusion. ST segment alterations resolved within 5 min. Maximum hsTNT measured during 48 h observation was 99 ng/L. In another case, not eligible as MAE, a small 3 × 3 mm thrombus at the right atrial puncture site was detected after successful PASCAL implantation and guide sheath retrieval. This was fully resolved after 4 weeks of oral anticoagulation while the patient remained asymptomatic.

During the average follow-up period of 8.7 ± 4.9 months, five patients (14%; 5/36) died. One patient died 29 days after

Figure 2 Mitral valve regurgitation (MR), functional status and biomarker results. PMVr by PASCAL repair system significantly reduced MR severity (A). MR reduction translates into improvement of NYHA functional class (B). Biomarkers were reduced at follow-up for both NT-proBNP (C) and hsTNT (D). Significant reduction of systolic echocardiographic derived pulmonary artery pressure (sPA) was measured at follow-up visit (E). Box plots represent median, 25–75th percentile, and min–max values. hsTNT, high-sensitive troponin T; NT-proBNP, NT-pro brain natriuretic peptide; NYHA, New York Heart Association.
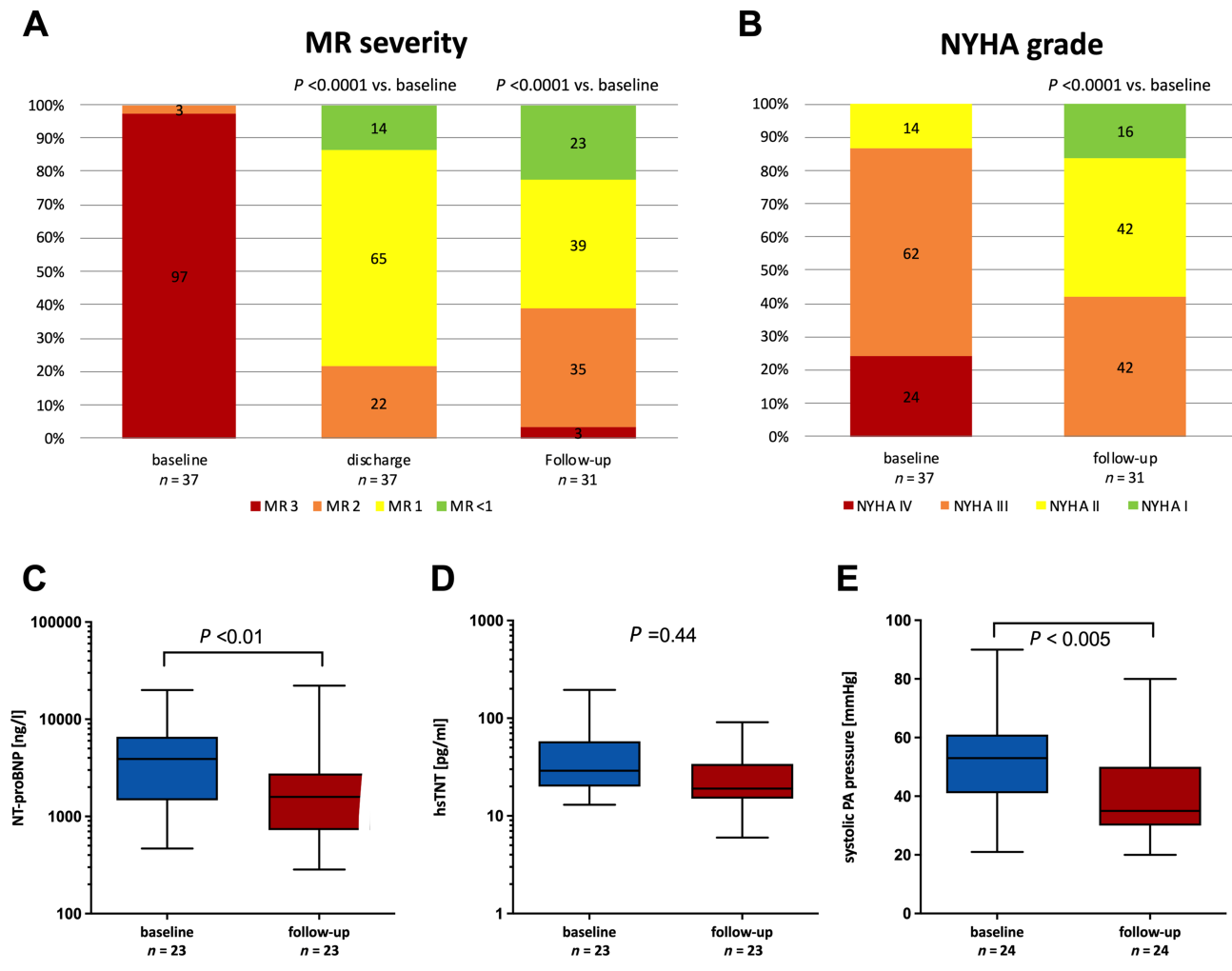
mitral leaflet repair due to a previously unknown progress of a chronic oncological disease. The patient decided actively against further surgical and oncological treatment and died under palliative care. Overall, two deaths, including the aforementioned, are attributable to oncological diseases. Three cases remain unclear but could well be attributed to cardiac disease due to advanced heart failure. Moreover, two of the patients were beyond 85 years of age. In one patient who had been evaluated for heart transplant before PASCAL intervention, the cardiac output remained severely impaired, requiring a left ventricular assist device implantation. Five patients had to be admitted to the hospital due to acute heart failure during follow-up. No cerebrovascular event or severe bleeding occurred during PASCAL implantation or follow-up. A detailed summary of MAEs is given in *Table 3*.

Discussion

Transcatheter mitral valve leaflet repair has become the standard therapy approach for severe MR in patients at high or prohibitive surgical risk. Novel interventional devices like the PASCAL mitral repair system hold promise to augment treatment possibilities in patients not eligible for current devices. In this context, the PASCAL device possesses several unique features, including the capability of independent leaflet grasping, a central spacer filling the regurgitant orifice area and a flexible nitinol backbone with broader shaped paddles aiming at reducing stress on the mitral leaflets.

This study represents the first analysis in an unselected single-centre real-life cohort providing results beyond a 6 month timeframe.[12] We analysed the acute safety and

Table 2 Follow-up parameters for all patients with successful PASCAL-based mitral valve repair ($n = 37$)

Follow-up outcome	
Follow-up (months) (mean ± SD)	8.73 ± 4.9
NYHA class at follow-up visit ($n = 31$)	
NYHA I (n/%)	5/16.1
NYHA II (n/%)	13/41.9
NYHA III (n/%)	13/41.9
NYHA IV (n/%)	0/0
MR at follow-up visit ($n = 31$)	
MR < 1 (n/%)	7/22.6
MR 1 (n/%)	12/38.7
MR 2 (n/%)	11/35.5
MR 3 (n/%)	1/3.2
Echocardiographic parameters ($n = 31$)	
LVEF (%) (median/IQR)	36/(20–46)
LVEDD (mm) (mean ± SD)	56.5 ± 8.6
LVESD (mm) (mean ± SD)	45.5 ± 12.5
MPG MV (mmHg) (mean ± SD)	2.8 ± 0.9
LA diameter (mm) (mean ± SD)	51 ± 7.0
sPA (mmHg) (mean ± SD)	42.8 ± 15.5
Biomarker ($n = 23$)	
NT-proBNP (ng/L) ($n = 23$; median/IQR)	1587/(725–2766)
hsTNT (pg/mL) ($n = 23$; median/IQR)	19 / (15–34)

hsTNT, high-sensitive troponin T; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; MPG MV, mean pressure gradient of the mitral valve; MR, mitral regurgitation; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association functional class; sPA: systolic pulmonary arterial pressure.

Table 3 Overview of procedural and follow-up major adverse events (MAE)

Procedural MAEs ($n = 41$)	
Air embolism (n/%)	1/2.4
Procedure related mortality (n/%)	0/0
Major vascular access complications (n/%)	0/0
Severe bleeding/Transfusion (n/%)	0/0
Cerebrovascular event (n/%)	0/0
Urgent cardiovascular surgery (n/%)	0/0
Composite procedural MAE (n/%)	**1/2.4**
Follow-up MAEs [$n = 36$ (1 × lost to FU)]	
All-cause mortality (n/%)	5/13.9
HF rehospitalization during follow-up (n/%)	5/13.9
Ventricular assist implantation (n/%)	1/2.8
Re-intervention for MR (n/%)	0/0
Cerebrovascular event (n/%)	0/0
Severe bleeding/Transfusion (n/%)	0/0
Composite follow-up MAE (n/%)	**12/30.6**

MAE rate of patients upon their last follow-up visit (on average 8.7 ± 4.9 months). HF, heart failure; MR, mitral regurgitation.

mid-term efficacy of PASCAL repair system-based MR repair in the first 41 patients treated with this novel device in our centre. Major findings of our study comprise (i) feasibility of PMVr using the PASCAL system with high technical, device, and procedural success rates also achieved in mitral valve anatomies beyond the EVEREST criteria and maintained over the mid-term follow-up period; (ii) safety of the procedure with low early and mid-term MAE rates; (iii) significant early and mid-term clinical improvement according to NYHA

functional class; and (iv) significant reduction of sPA and NT-proBNP levels without translating into significant cardiac remodelling or improved LVEF at mid-term follow-up.

Patients included in our study represent an unselected all-comer population with an advanced state of disease. This is evidenced by a lower baseline LVEF (38% vs. 45%) and higher NT-proBNP (4353 vs. 4148 ng/L) compared with the highly selected population in the CLASP trial.[6,7] Even in comparison with recently published experiences from real-world data reporting LVEF values from 41% to 47%,[8,12–14] our cohort represents a severer impaired systolic function.

In this challenging cohort, successful PASCAL device implantation could be achieved in 90% of patients (37/41) with numerically higher technical success (100%; 12/12; $P = 0.54$) in patients presenting with degenerative MR compared with functional MR. Procedural failure was mainly due to aborted implantation in four cases of complex anatomies, including a bail out procedure where predominantly elevated transvalvular gradients resulted in abortion of the procedure. This is slightly below the 95% reported in the CLASP trial.[6,7] Other than expected, the non-successful procedures occurred in later cases and are thus not attributable to a learning curve. Yet a similar finding was described in the multicentre analysis by Mauri *et al*. and is most probably attributable to a more liberal patient selection with growing device experience.[14]

Implantation of the PASCAL implant resulted in a significant acute reduction of MR severity with 100% of patients being discharged with an MR grade ≤ 2. In 86% of patients (32/37), one PASCAL device was sufficient to achieve this result. Twelve patients undergoing PASCAL intervention (12/41, 29%) presented with complex and challenging mitral valve anatomies, which would not be considered suitable for MitraClip therapy according to the EVEREST criteria.

The implantation procedure proved safe with a MAE and all-cause mortality rate of 3%, each. No cardiovascular deaths occurred within 30 days after PMVr. Notably, the case of periinterventional air embolism, which resolved without any sequelae, resulted in a modification of the instructions for use of the PASCAL repair system. After modification of the de-airing procedure, no further cases of air-embolism occurred.

Acute and discharge results of our patient cohort are in line with previously published data of the CLASP study[6,7] and early real-world single and multicentre reports,[8,12–14] achieving 95–100% technical success rates resulting in 5–8% 30 day MAEs and a 3% all-cause mortality rate, respectively. Unlike previous reports, implantation of a single PASCAL device was sufficient to achieve optimal MR reduction in a large proportion of our patients (86%). In the CLASP study, 49% of patients were treated with two PASCAL devices,[7] and in the real-world analysis of Besler *et al*., 48% of patients received more than one device.[13] However, the recently published retrospective real-world analysis of Barth *et al*. reports the use

of only one PASCAL device in 69% of patients (20/29), which is well in line with our findings. Compared with a propensity-score matched MitraClip cohort treated in the same centre [one Clip approach sufficient in 10/29 patients (34.5%)], significantly fewer devices were necessary if the PASCAL repair system was used.[12] The reduced number of required PASCAL devices is presumably related to the broader shape of the device and the aforementioned novel device features enabling optimized and augmented leaflet insertion as well as filling of the regurgitant orifice area.

During the follow-up period of 8.7 months, MR reduction was maintained with 97% of patients presenting MR ≤ 2. Neither early nor late single-leaflet device attachment was found. Persisting successful PMVr translated into a significant and sustained improvement of NYHA functional class with 58% of our patients presenting in NYHA class II or below at the time of latest follow-up visit. To the best of our knowledge, this is the longest follow-up in a real-world setting using the PASCAL repair system for PMVr published so far. It proves mid-term efficiency of this intervention, expanding the existing knowledge from short-term follow-up data based on previous studies.[7,8,12–15] Moreover, successful PMVr using the PASCAL device resulted in a significant reduction of sPA. sPA is of prognostic relevance and indicates a reduction of post-capillary pressure, which in turn is associated with a favourable outcome after PMVr.[16,17] This is further underlined by the significant reduction of NT-proBNP and numerical reduction of hsTNT at follow-up, highlighting the sustained reduction of cardiac stress.

However, contrary to the 1 year follow-up results of the CLASP trial,[6] MR reduction did not translate into significant reverse cardiac remodelling within the analysed timeframe in spite of improved functional class and biomarkers. This seems attributable to several factors: (i) the severely impaired LV function in our cohort which might delay reverse remodelling, (ii) the more heterogeneous cohort including patients with degenerative origin of MR and preserved LVEF, and (iii) the lower absolute patient number. Consistently, neither 30 day data from Besler *et al*.[13] nor analysis of our early real-life experience with the MitraClip device could detect significant cardiac remodelling before 1 year follow-up.[18] Given the positive effects of PMVr despite progressive LV dilation in the COAPT trial, there remains a need for further investigation in significance of reverse cardiac remodelling in PMVr.[19]

Overall, the results of our study are well comparable with current evidence from both, the CLASP trial[6,7] and first retrospective short-term analyses of real-world patient cohorts.[8,12–15] Thus, specific advantages of the PASCAL mitral repair system may add additional possibilities for individualized mitral valve repair tailoring procedures to the unique anatomical features and underlying pathologies in each patient.

To further elucidate advantages and shortcomings of the novel PASCAL transcatheter valve repair system, a direct comparison with the current MitraClip devices is necessary. In this context, the CLASP IID/IIF trial is currently recruiting patients to compare safety and effectiveness of these devices in patients with degenerative and functional MR (NCT03706833).

Limitations to the study

This is a single-centre, retrospective study analysing a limited number of patients. Moreover, the lack of an external core lab adjudicating the events may bias data interpretation. In addition, only the first-generation PASCAL device has been employed in this study. Meanwhile, in the context of accelerated product improvement, in addition to this device, the PASCAL Ace system has been introduced, featuring a narrower design profile. However, despite these limitations, the novel data indicate that PMVr using the PASCAL device in high-risk patients presenting with severe MR is feasible, safe, and effective and represents an alternative treatment option for the anatomic variety of pathologies causal for severe MR.

Conclusion

In high-risk patients presenting with severe MR, PMVr with the PASCAL repair system is feasible and safe. Successful interventional leaflet repair results in persistent mid-term MR reduction as well as clinical improvement.

Conflict of interest

Prof Raake has received speaker honoraria from Abbott Cardiovascular and Edwards Lifesciences. Prof Frey has received speaker honoraria from Edwards Lifesciences. Prof Kreusser has received research funding from Abbott Cardiovascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Funding

Supporting information

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

Table S1. Anatomical MV characteristics of patients with aborted implant procedures. In 4/41 cases PASCAL device could not be implanted due to a prohibitive mean transmitral gradient (MPG) after leaflet grasping and device closure. To allow better interpretation of possible indicators for device failure a detailed anatomical description is provided here. MR: mitral regurgitation, MVA: mitral valve orifice area, AML: anterior mitral leaflet, PML: posterior mitral leaflet, CABG: coronary artery bypass graft, MVr: surgical mitral valve reconstruction, SAVR: surgical aortic valve replacement.

Table S2. Baseline characteristics and follow-up outcomes of all patients treated "per protocol" (successful PASCAL implantation and follow-up visit). NYHA: New York Heart Association functional class, NT-pro-BNP: n-terminal pro brain natriuretic peptide, ICD: implantable cardiac defibrillator, CRT: cardiac resynchronization therapy, MR: mitral regurgitation, LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, MPG MV: mean pressure gradient of the mitral valve, LA: left atrial, sPA: systolic pulmonary arterial pressure. #: n = 23 for hsTNT and NT-proBNP (see also Figure 2).

Figure S1. Mitral valve regurgitation (MR) and clinical functional status in patients undergoing "per protocol" intervention and follow-up. PMVr by PASCAL repair system significantly reduced MR severity (A). MR reduction translates into improvement of NYHA functional class (B).

References

1. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, Simioniuc A, Gullace M, Ghio S, Enriquez-Sarano M, Temporelli PL. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 2011; **97**: 1675–1680.

2. Dziadzko V, Clavel MA, Dziadzko M, Medina-Inojosa JR, Michelena H, Maalouf J, Nkomo V, Thapa P, Enriquez-Sarano M. Outcome and undertreatment of mitral regurgitation: a community cohort study. *Lancet* 2018; **391**: 960–969.

3. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006; **368**: 1005–1011.

4. Moore M, Chen J, Mallow PJ, Rizzo JA. The direct health-care burden of valvular heart disease: evidence from US national survey data. *Clinicoecon Outcomes Res* 2016; **8**: 613–627.

5. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L, Investigators EI. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 2011; **364**: 1395–1406.

6. Webb John G, Hensey M, Szerlip M, Schäfer U, Cohen Gideon N, Kar S, Makkar R, Kipperman Robert M, Spargias K, O'Neill William W, Ng Martin KC, Fam Neil P, Rinaldi Michael J, Smith Robert L, Walters Darren L, Raffel Christopher O, Levisay J, Latib A, Montorfano M, Marcoff L, Shrivastava M, Boone R, Gilmore S, Feldman Ted E, Lim DS. 1-year outcomes for transcatheter repair in patients with mitral regurgitation from the CLASP study. *JACC: Cardiovasc Interv* 2020; **13**: 2344–2357.

7. Lim DS, Kar S, Spargias K, Kipperman RM, O'Neill WW, Ng MKC, Fam NP, Walters DL, Webb JG, Smith RL, Rinaldi MJ, Latib A, Cohen GN, Schäfer U, Marcoff L, Vandrangi P, Verta P, Feldman TE. Transcatheter valve repair for patients with mitral regurgitation: 30-day results of the CLASP study. *JACC Cardiovasc Interv* 2019; **12**: 1369–1378.

8. Kriechbaum SD, Boeder NF, Gaede L, Arnold M, Vigelius-Rauch U, Roth P, Sander M, Boning A, Bayer M, Elsasser A, Mollmann H, Hamm CW, Nef HM. Mitral valve leaflet repair with the new PASCAL system: early real-world data from a German multicentre experience. *Clin Res Cardiol* 2020; **109**: 549–559.

9. Writing Committee M, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, O'Gara PT, Rigolin VH, Sundt TM 3rd, Thompson A, Toly C. 2020 ACC/AHA guideline for the Management of Patients with Valvular Heart Disease: a report of the american College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol* 2021; **77**: e25–e197.

10. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, Schofer J, Cutlip DE, Krucoff MW, Blackstone EH, Genereux P, Mack MJ, Siegel RJ, Grayburn PA, Enriquez-Sarano M, Lancellotti P, Filippatos G, Kappetein AP, Mitral Valve Academic Research C. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles: a consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol* 2015; **66**: 278–307.

11. Stone GW, Adams DH, Abraham WT, Kappetein AP, Genereux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS, Mitral Valve Academic Research C. linical 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. Barth S, Hautmann MB, Arvaniti E, Kikec J, Kerber S, Zacher M, Halbfass P, Ranosch P, Lehmkuhl L, Foldyna B, Lusebrink U, Hamm K. Mid-term hemodynamic and functional results after transcatheter mitral valve leaflet repair with the new PASCAL device. *Clin Res Cardiol* 2021; **110**: 628–639.

13. Besler C, Noack T, von Roeder M, Kitamura M, Kresoja KP, Flo Forner A, Bevilacqua C, Desch S, Ender J, Borger MA, Thiele H, Lurz P. Transcatheter edge-to-edge mitral valve repair with the PASCAL system: early results from a real-world series. *EuroIntervention* 2020; **16**: 824–832.

14. Mauri V, Besler C, Riebisch M, Al-Hammadi O, Ruf T, Gercek M, Horn P, Grothusen C, Mehr M, Becher MU, Mues C, Boeder N, Kreidel F, Friedrichs K, Westenfeld R, Braun D, Ozturk C, Baldus S, Rassaf T, Thiele H, Nickenig

G, Hausleiter J, Mollmann H, Kelm M, Rudolph V, von Bardeleben RS, Nef HM, Luedike P, Lurz P, Pfister R. German multicenter experience with a new leaflet-based transcatheter mitral valve repair system for mitral regurgitation. *JACC Cardiovasc Interv* 2020; **13**: 2769–2778.

15. Praz F, Spargias K, Chrissoheris M, Bullesfeld L, Nickenig G, Deuschl F, Schueler R, Fam NP, Moss R, Makar M, Boone R, Edwards J, Moschovitis A, Kar S, Webb J, Schafer U, Feldman T, Windecker S. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. *Lancet* 2017; **390**: 773–780.

16. Greiner S, Jud A, Aurich M, Geisenberger C, Uhlmann L, Hilbel T, Kieser M, Katus HA, Mereles D. Prognostic relevance of elevated pulmonary arterial pressure assessed non-invasively: Analysis in a large patient cohort with invasive measurements in near temporal proximity. *PLoS One* 2018;**13**: e0191206.

17. Koell B, Ludwig S, Bhadra O, Gossling A, Schofer N, Schirmer J, Conradi L, Reichenspurner H, Blankenberg S, Lubos E, Kalbacher D. Acute hemodynamic changes and long term prognostic impact of pulmonary hypertension in patients undergoing percutaneous mitral valve edge to edge repair. *Eur Heart J* 2020; **41**.

18. Pleger ST, Schulz-Schonhagen M, Geis N, Mereles D, Chorianopoulos E, Antaredja M, Lewening M, Katus HA, Bekeredjian R. One year clinical efficacy and reverse cardiac remodelling in patients with severe mitral regurgitation and reduced ejection fraction after MitraClip implantation. *Eur J Heart Fail* 2013; **15**: 919–927.

19. 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, Weissman NJ, Mack MJ, Investigators C. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018; **379**: 2307–2318.