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Transcatheter and Surgical Management of Mitral Paravalvular Leak

Long-Term Outcomes

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CME/MOC Objective for This Article: At the end of the activity the reader should be able to: 1) recognize the contemporary percutaneous and surgical techniques used to treat mitral PVL; 2) identify the short and long-term outcomes of patients undergoing surgical or percutaneous mitral PVL; and 3) define the advantages and the limitations of each treatment approach.

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ABSTRACT

OBJECTIVES The aim of this study was to report the use trends and immediate and long-term outcomes of a large cohort of patients who underwent redo surgery or transcatheter repair of paravalvular leaks (PVLs) at a tertiary referral center.

BACKGROUND Percutaneous treatment of mitral PVL has emerged as an alternative to surgical treatment in high-risk surgical candidates. There are limited data on the utilization trends, safety, and efficacy of both procedures in the management of mitral PVL.

METHODS Patients who underwent treatment of mitral PVL at the Mayo Clinic between January 1995 and December 2015 were enrolled. Utilization trends, procedural details, technical success, and in-hospital and long-term outcomes were assessed.

RESULTS Three hundred eighty-one patients underwent percutaneous ($n = 195$) or surgical ($n = 186$) treatment of mitral PVLs. The mean age was 66 ± 12 years, and 37% of patients had bioprosthetic valves. Technical success was higher in the surgical group (95.5% vs. 70.1%; $p < 0.001$). In-hospital major adverse events were more common after surgery (22.5% vs. 7.7%; $p < 0.001$). In-hospital death occurred in 3.1% and 8.6% of patients undergoing percutaneous and surgical treatment, respectively ($p = 0.027$). However, in a multivariate logistic regression analysis, only active endocarditis, chronic renal failure, and severe mitral annular calcifications were significant predictors of in-hospital mortality. Reintervention rates were similar (11.3% vs. 17.2% in the percutaneous and surgical groups, respectively; $p = 0.10$), with the majority of reinterventions in the percutaneous group occurring early because of residual leak or persistent hemolysis. After risk adjustment, there was no significant difference in long-term survival between patients who underwent surgical versus transcatheter treatment of PVLs.

CONCLUSIONS In contemporary practice, patients with symptomatic mitral PVLs are best treated with an integrated team approach incorporating both surgical and percutaneous techniques. Patient selection and timing of intervention are critical to achieve optimal results. (J Am Coll Cardiol Intv 2017;10:1946–56) © 2017 by the American College of Cardiology Foundation.

Paravalvular leak (PVL) is a not uncommon complication after mitral valve replacement, with reported incidence rates of 7% to 17% (1–3). Although the majority of PVLs are subclinical, about 3% of patients develop severe heart failure, hemolysis, or a combination of both requiring intervention (4–6). For symptomatic patients, repeat surgery has been the traditional treatment for PVL, but it carries an excess risk for morbidity and mortality and has been associated with variable results (6,7). Percutaneous repair of PVL has emerged as an attractive and less invasive alternative to surgical repair with promising immediate and midterm results (8–10).

The aim of this study was to assess the utilization trends and immediate and long-term outcomes of a large cohort of patients who underwent redo surgery or transcatheter repair of PVLs at a tertiary referral center.

METHODS

STUDY POPULATION. The Mayo Clinic Institutional Review Board approved the study. We retrospectively identified patients who underwent percutaneous or

ABBREVIATIONS AND ACRONYMS

AVP-II = Amplatzer Vascular Plug II

CI = confidence interval

PVL = paravalvular leak

surgical intervention for mitral PVLs at the Mayo Clinic (Rochester, Minnesota) between January 1995 and December 2015. Percutaneous repair techniques have evolved over the past decade, which had a major impact on the treatment of PVLs at our institution. The indications for percutaneous repair were severe dyspnea with moderate or severe PVL and clinically significant hemolytic anemia. Clinically significant hemolytic anemia was defined as symptomatic anemia (hemoglobin <11 g/dl in women and <12.5 g/dl in men), with laboratory evidence of intravascular hemolysis with or without repeat transfusions. All patients who were treated before January 2006 (when PVL percutaneous repair became available) were referred for surgical intervention.

SEE PAGE 1957

After January 2006, criteria to refer patients for redo operation at the outset were: 1) active endocarditis; 2) a very large leak involving more than one-half of the circumference of the sewing ring; 3) rocking motion or instability of the prosthesis; and 4) need for concomitant surgical intervention. Patients who did not meet 1 of these criteria and those deemed at very high risk for reoperation were referred for percutaneous closure.

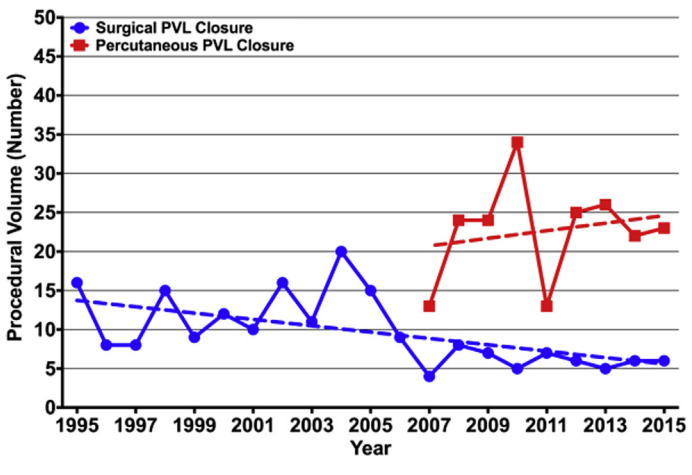
PVL REPAIR TECHNIQUES. Percutaneous techniques. In the majority of patients, the antegrade transseptal approach was used to cannulate the PVLs. Most defects were closed with the Amplatzer Vascular Plug II (AVP-II, St. Jude Medical, St. Paul, Minnesota). Other devices, including the Amplatzer Duct Occluder, Amplatzer Septal Occluder, and Amplatzer Muscular VSD Occluder (all manufactured by St. Jude Medical), were also used but less frequently. Several techniques were used depending on the size, number, and location of the PVL: single device placement, simultaneous (double-wire) deployment, sequential deployment, and sequential deployment using an arteriovenous or transapical rail. The details of these techniques have been previously described (11).

Surgical techniques. Patients who underwent repeat operations had surgical repair of PVLs with either a patch or pledgeted suture repair depending on the quality of the tissues. When repair was not possible, re-replacement of the mitral valve with a biological or a mechanical prosthesis was performed. The severity of the mitral PVL, before and immediately after the procedure, was graded semiquantitatively using Doppler echocardiography and color-flow imaging (grade I, mild; grade II, moderate; grade III, severe) by echocardiographers experienced in the intraoperative assessment of prosthetic mitral valve (9).

STUDY ENDPOINTS. The primary efficacy endpoint was technical success, defined according to the consensus document from the Paravalvular Leak Academic Research Consortium: absence of procedural mortality or stroke; successful access, delivery, and retrieval of the device delivery system; proper placement and positioning device(s); freedom from unplanned surgical or interventional procedures related to the device or access procedure; continued intended safety and performance of the device, including no evidence of structural or functional failure of the prosthetic valve; no specific device-related technical failure issues and complications; and reduction of regurgitation to no greater than mild (1+) paravalvular regurgitation (and without associated hemolysis) (12). The primary safety endpoint was freedom from in-hospital death and major adverse events (stroke, vascular complications, renal failure requiring dialysis, pneumonia, prolonged ventilation, hemothorax, tamponade, and device embolization requiring urgent surgery). Secondary endpoints were reintervention rates over time and long-term freedom from death in patients who underwent surgical treatment compared with those who underwent surgical treatment after a failed percutaneous treatment attempt.

DATA ANALYSIS. Procedural, in-hospital, and long-term outcomes were assessed by retrospective chart review. The Mayo Clinic maintains an updated registry of long-term mortality for patients undergoing invasive procedures, including PVL repair. Continuous

FIGURE 1 Temporal Trend of Paravalvular Leak Closure by Treatment Modality



PVL = paravalvular leak.

TABLE 1 Characteristics of Patients Undergoing Mitral Paravalvular Leak Closure

	All Patients (N = 381)	Percutaneous PVL Closure (n = 195)	Surgical PVL Closure (n = 186)	p Value
Age, yrs	65.7 ± 12.1	67.5 ± 12.5	63.8 ± 11.4	0.003
Female	172 (45.1)	89 (45.6)	83 (44.6)	0.84
Presenting symptoms				
Heart failure functional class: NYHA III or IV	276 (72.4)	152 (77.9)	124 (66.7)	0.01
Hemolysis	155 (40.7)	83 (43.2)	72 (38.7)	0.37
Both	107 (28.1)	61 (31.3)	46 (24.7)	0.13
Mitral valve surgery				
Time from surgery to repair, month	85.1 ± 115.6	57.0 ± 85.7	115.6 ± 134.8	<0.001
Bioprosthetic valve	141 (37.0)	78 (40.0)	63 (33.9)	0.22
Number of sternotomies	2.3 ± 1.1	1.9 ± 1.0	2.7 ± 0.9	<0.001
Medical comorbidities				
Chronic pulmonary disease	52 (13.6)	31 (15.9)	21 (11.7)	0.24
Atrial fibrillation/flutter	253 (66.4)	141 (72.3)	112 (60.2)	0.02
Chronic renal insufficiency	142 (37.3)	62 (31.8)	80 (43.0)	0.02
Previous CABG	99 (26.0)	50 (25.6)	49 (26.3)	0.88
Previous endocarditis	92 (24.1)	39 (20.0)	53 (28.5)	0.053
Active endocarditis	7 (1.8)	0 (0.0)	7 (3.8)	0.006
Chronic steroid	25 (6.6)	12 (6.2)	13 (7.0)	0.74
Rheumatic heart disease	142 (37.3)	47 (24.1)	95 (51.1)	<0.001
Prior chest radiation	16 (4.2)	14 (7.2)	2 (1.1)	0.003
Prior permanent pacemaker	92 (24.1)	68 (34.9)	24 (12.9)	<0.001
Prior implantable defibrillator	16 (4.2)	9 (4.6)	7 (3.8)	0.68

Values are mean ± SD or n (%).
CABG = coronary artery bypass grafting; NYHA = New York Heart Association; PVL = paravalvular leak.

TABLE 2 Baseline Echocardiographic Findings in Patients Undergoing Mitral Paravalvular Leak Closure

	All Patients (N = 381)	Percutaneous PVL Closure (n = 195)	Surgical PVL Closure (n = 186)	p Value
Paravalvular leak grade				
Mild (grade I)	0 (0.0)	0 (0.0)	0 (0.0)	0.78
Moderate (grade II)	51 (13.4)	27 (14.0)	24 (12.9)	
Severe (grade III)	328 (86.1)	166 (86.0)	162 (87.1)	
Number of mitral paravalvular leaks	1.4 ± 0.7	1.3 ± 0.6	1.5 ± 0.9	0.008
Number of PVLs ≤2	348 (91.3)	186 (95.4)	162 (87.1)	0.004
Location of the leak				
Medial	86 (22.6)	50 (26.2)	36 (20.2)	<0.001
Lateral	54 (14.2)	35 (18.3)	19 (10.7)	
Anterior	114 (29.9)	41 (21.5)	73 (41.0)	
Posterior	47 (12.3)	15 (7.9)	32 (18.0)	
Multiple jets	68 (17.8)	50 (26.2)	18 (10.1)	
Severe mitral annular calcification	86 (22.6)	40 (20.5)	46 (24.7)	0.33
Left ventricular ejection fraction, %	59.3 ± 12.0	61.0 ± 12.0	57.0 ± 12.0	0.006
Left ventricular ejection fraction <50%	62 (16.3)	28 (14.4)	34 (18.3)	0.50
Left ventricular end-diastolic dimension, mm	52.7 ± 7.8	52.0 ± 8.0	53.0 ± 8.0	0.21
Left ventricular end-systolic dimension, mm	35.0 ± 8.5	35.0 ± 8.0	35.0 ± 9.0	0.85
Severe tricuspid regurgitation	118 (31.0)	54 (32.9)	64 (36.6)	0.48
Right ventricular systolic pressure, mm Hg	58.2 ± 18.8	58.0 ± 18.0	59.0 ± 20.0	0.46
Severe pulmonary hypertension	249 (65.4)	133 (68.2)	116 (62.2)	0.23

Values are n (%) or mean ± SD.
PVL = paravalvular leak.

TABLE 3 Percutaneous Mitral Paravalvular Leak Repair Procedural Details

	Percutaneous PVL Closure (n = 195)
Closure technique	
Transseptal without VA rail	128 (65.6)
Transseptal with VA rail	52 (26.7)
Transseptal with TA rail	15 (7.7)
Closure device	
AVP-II	138 (70.8)
ADO	13 (6.7)
ASO	10 (5.1)
Other/combinations	18 (9.2)
Device placed across defect	179 (91.8)
Number of device placed	1.6 ± 1.1
Fluoroscopy time, min	58 ± 28
Contrast load, ml	21 ± 32

Values are n (%) or mean ± SD.
ADO = Amplatzer Ductal Occluder; ASO = Amplatzer Septal Occluder; AVP-II = Amplatzer Vascular Plug II; PVL = paravalvular leak; TA = transapical; VA = venoarterial.

parameters of the study groups were compared using the Student *t* test. For comparison of categorical data, we used the chi-square or Fisher exact test. Binary logistic regression analysis was used to identify variables independently associated with: 1) in-hospital death; and 2) technical failure. All analyses were performed with SPSS version 22 (IBM, Armonk, New York). Statistical significance was inferred at $p \leq 0.05$.

Risk factors for in-hospital mortality were assessed using univariate and multivariate logistic regression to estimate odds ratios and their associated 95% confidence intervals (CIs). Factors found to have p values <0.10 in the univariate analysis were included in the multivariate model and assessed in a stepwise fashion. In an effort to create a parsimonious model and avoid overfitting due to the low event rate (n = 22), only the 3 most statistically significant factors were included in the final model.

We then estimated the association between treatment approach to the PVL (surgical or transcatheter) and mortality (1-year and overall) using a Cox proportional hazards model to estimate hazard ratios and 95% CIs. Person-time was calculated from the date of PVL treatment to either death or the last date of available follow-up. The hazard ratio was stratified by treatment approach and adjusted for baseline characteristics including age, chronic obstructive pulmonary disease, severe mitral annular calcification, chronic kidney disease, congestive heart failure, and active bacterial endocarditis in a stepwise fashion.

TABLE 4 Surgical Mitral Paravalvular Leak Repair Procedural Details

	Surgical PVL Closure (n = 186)
Surgical procedure	
Mitral valve re-replacement	93 (50.0)
Patch repair of PVL	4 (2.2)
Two-layer suture repair	14 (7.5)
Single-layer pledgeted repair	75 (40.3)
Surgical technique	
Transseptal approach	79 (42.5)
LA standard approach	91 (48.9)
Superior septal (dome) approach	15 (8.1)
Transventricular MVR	1 (0.5)
Concomitant surgery	117 (62.9)
Concomitant tricuspid valve surgery	64 (34.4)
Aortic cross-clamp time, min	71 ± 45
Cardiopulmonary bypass time, min	119 ± 60

Values are n (%) or mean ± SD.
LA = left atrial; MVR = mitral valve replacement; PVL = paravalvular leak.

TABLE 5 Univariate Predictors of Moderate or Greater Residual Leak in Patients Undergoing Percutaneous Paravalvular Leak Closure

	Odds Ratio	95% CI	p Value
History of endocarditis	1.63	0.78–3.39	0.19
>1 PVL	1.39	0.71–2.72	0.33
Medial PVL location	1.26	0.63–2.50	0.52
Mechanical valve	1.41	0.75–2.68	0.29
Severe mitral annular calcification	1.01	0.47–2.15	0.99
Rheumatic heart disease	0.53	0.27–1.06	0.07

CI = confidence interval; PVL = paravalvular leak.

RESULTS

Three hundred eighty-one patients underwent percutaneous (n = 195) or surgical (n = 186) treatment of mitral PVLs during the study period. After the introduction of percutaneous PVL repair techniques, the majority of patients were treated using an integrated multidisciplinary approach including both surgical and percutaneous treatment (Figure 1). The mean age was 66 ± 12 years, 45% of patients were women, and 37% had bioprosthetic valves. In-hospital data were available for all patients, and long mortality data were available for 98.2% of patients. Mean time from index surgery to PVL repair was 85.1 ± 115.6 months and differed significantly between the percutaneous group (57.0 ± 85.7 months) and the surgical group (116 ± 135 months). Comorbidities were common but also differed between the 2 groups (Table 1). The mean number of PVLs was 1.4 ± 0.7. Anterior location was the most common location of the PVL (30%) (Table 2). Mean left ventricular

TABLE 6 In-Hospital and Long-Term Outcomes of Patients Undergoing Surgical or Percutaneous Paravalvular Leak Closure

	All Patients (N = 381)	Percutaneous PVL Closure (n = 195)	Surgical PVL Closure (n = 186)	p Value
Residual leak				<0.001
None	206 (54.1)	78 (40.2)	128 (82.6)	
Mild (grade I)	78 (20.5)	58 (29.9)	20 (12.9)	
Moderate (grade II)	41 (10.8)	36 (18.6)	5 (3.2)	
Severe (grade III)	24 (6.3)	22 (11.3)	2 (1.3)	
In-hospital death	22 (5.8)	6 (3.1)	16 (8.6)	0.027
In-hospital major adverse events	57 (15.0)	15 (7.7)	42 (22.6)	<0.001
Stroke	6 (1.6)	2 (1.0)	4 (2.2)	0.38
Vascular complications	7 (1.8)	6 (3.1)	1 (0.5)	0.14
Renal failure requiring dialysis	15 (3.9)	1 (0.5)	14 (7.5)	<0.001
Prolonged ventilation	3 (0.8)	0 (0.0)	3 (1.6)	0.08
Pneumonia	17 (4.5)	0 (0.0)	17 (9.1)	<0.001
Tamponade	4 (1.0)	1 (0.5)	3 (1.6)	0.58
Hemothorax/bronchial bleeding*	4 (1.0)	4 (2.1)	0 (0.0)	0.12
Embolization needing surgery†	1 (0.3)	1 (0.5)	NA	NA
Hospital length of stay, days	9.1 ± 10.2	5.3 ± 7.6	14.0 ± 11.0	<0.001
Follow-up available, yrs	4.0 ± 3.9	3.7 ± 2.7	7.4 ± 5.7	<0.001
Overall mortality	225 (59.0)	98 (50.3)	127 (68.3)	<0.001
Reintervention	54 (14.2)	22 (11.3)	32 (17.2)	0.10
Reoperation	38 (10.0)	20 (9.7)	19 (10.3)	0.88
Repeat percutaneous intervention	22 (5.8)	5 (2.6)	17 (9.1)	0.006
Time to reintervention, month	28.2 ± 38.6	6.2 ± 7.4	42.8 ± 43.8	<0.001

Values are n (%) or mean ± SD. *Three patients had hemothorax after transapical access. †Four patients in total had device embolization; 3 were snared percutaneously and only 1 required open surgical intervention.

PVL = paravalvular leak.

ejection fraction was 59 ± 12%. Mean right ventricular systolic pressure was 58.2 ± 18.8 mm Hg.

The most common percutaneous PVL repair techniques were transseptal without venoarterial rail (65%) and transseptal with venoarterial rail (27%) (Table 3). Most patients (71%) were treated with AVP-II devices (mean number of devices 1.6 ± 1.1). Fluoroscopy time was 58 ± 28 min, and contrast load was 21 ± 32 ml. The most common surgical PVL treatment techniques were mitral valve re-replacement (50%) and multiple pledgeted suture repair (40%). There was no significant difference in the type of surgical procedure (repair vs. replacement) over time (Online Figure 1). The most common surgical approach was through a standard left atriotomy (49%) (Table 4). Concomitant cardiac surgery was performed in 63% of patients. The mean cardiopulmonary bypass time was 119 ± 60 min, and the mean aortic cross-clamp time was 71 ± 45 min.

The technical success rate was higher in the surgical group compared with the percutaneous group (95.5% vs. 70.1%, respectively; $p < 0.001$). There were no statistically significant predictors of technical failure in patients who underwent percutaneous PVL repair (Table 5). Major adverse events occurred more frequently after surgery (22.5% vs. 7.7%; $p < 0.001$). Acute kidney injury, pneumonia, and stroke were the most common complications after surgery, whereas vascular complications and hemothorax related to apical access were the most common complications after percutaneous repair (Table 6). Mean hospital length of stay was 5.3 ± 7.6 days in the percutaneous group and 14.0 ± 11.0 days in the surgical group ($p < 0.001$).

In-hospital death occurred in 3.1% and 8.6% of patients undergoing percutaneous and surgical

TABLE 7 Univariate Logistic Regression for Predictors of In-Hospital Mortality in Patients Undergoing Paravalvular Leak Closure

	Odds Ratio	95% CI	p Value
Age	1.03	0.99-1.08	0.16
Female	0.83	0.37-2.21	0.91
Time to repair	1.00	1.00-1.01	0.006
NYHA functional class III or IV heart failure	8.13	1.08-61.3	0.04
Creatinine >1.5 mg/dl	7.99	2.63-24.26	<0.001
Active infective endocarditis	28.00	5.80-135.13	<0.001
Severe mitral annular calcification	2.76	1.12-6.78	0.03
Surgical treatment	3.58	1.28-9.97	0.02

CI = confidence interval; NYHA = New York Heart Association.

TABLE 8 Multivariate Logistic Regression for Predictors of In-Hospital Mortality in Patients Undergoing Paravalvular Leak Treatment

	Odds Ratio	95% CI	p Value
Active infective endocarditis	16.36	3.09–86.55	0.001
Creatinine >1.5 mg/dl	6.00	1.90–18.92	0.002
Severe mitral annular calcification	3.18	1.19–8.53	0.02

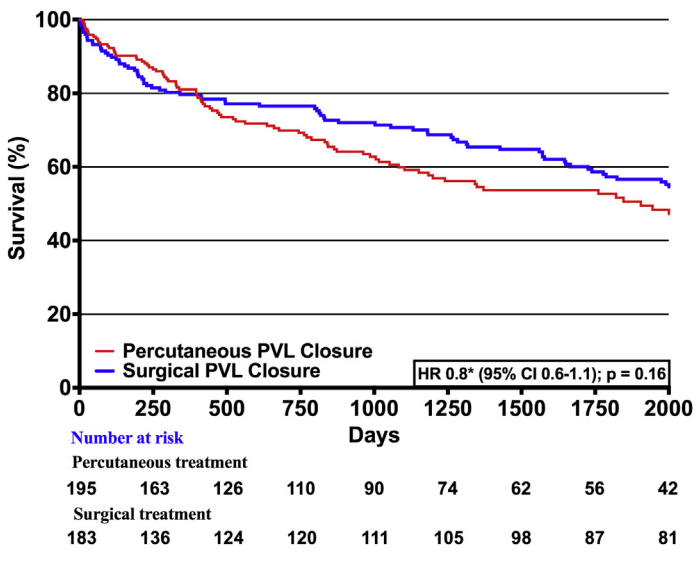
CI = confidence interval.

treatment, respectively (p = 0.027). However, in a multivariate logistic regression analysis, active endocarditis (odds ratio: 16.4; 95% CI: 3.09 to 86.55), chronic renal failure (odds ratio: 6.0; 95% CI: 1.90 to 18.92), and severe mitral annular calcifications (odds ratio: 3.2; 95% CI: 1.19 to 8.53) were the only significant predictors of in-hospital mortality in the overall cohort (Tables 7 and 8). After adjusting for age, chronic obstructive lung disease, mitral annular calcifications, chronic kidney disease, congestive heart failure, and active endocarditis, there was no significant difference in long-term survival between patients who underwent surgical versus transcatheter treatment of PVLs (adjusted hazard ratio: 0.8; 95% CI: 0.6 to 1.1; p = 0.16) (Figure 2, Table 9). Age, serum creatinine >1.5 mg/dl, severe mitral annular calcifications, chronic obstructive lung disease, active endocarditis, and New York Heart Association functional class III or IV heart failure were the strongest predictors of long-term mortality. These variables were also the strongest predictors of 1-year mortality, with the exception of chronic obstructive lung disease (Online Table 1).

Patients who had percutaneous treatment failure, who subsequently underwent surgical treatment, had similar long-term survival compared with patients who underwent surgical treatment at the outset (Figure 3). The need for subsequent surgical treatment significantly decreased with increasing experience with percutaneous PVL closure (Figure 4).

Fifty-four patients (14.2%) required repeat interventions for persistent or recurrent symptomatic PVLs. In the percutaneous group, the majority of repeat interventions were early reoperations due to failure of percutaneous repair or persistent hemolysis. Among patients who underwent initial percutaneous PVL closure attempts and required subsequent surgical repair, all subsequent surgical procedures occurred within 1.5 years (mean 0.36 ± 0.50 years) (Online Figure 2). In the surgical group, the majority of repeat interventions were required because of recurrence of PVLs and occurred at a mean of 2.3 years; all occurred within 9.4 years (Table 6).

FIGURE 2 Long-Term Mortality Following Surgical and Percutaneous Mitral Paravalvular Leak Closure



*Reference: percutaneous treatment; hazard ratio (HR) adjusted for age, COPD, MAC, CKD, CHF, and active endocarditis. CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; MAC = mitral annular calcification; PVL = paravalvular leak.

DISCUSSION

The principal findings of the present investigation are as follows: 1) in contemporary practice, percutaneous repair is feasible in the majority of cases and is being increasingly used in the management of patients with severe symptomatic PVLs; 2) surgical treatment of mitral PVLs achieves higher rates of complete or near complete obliteration of PVLs compared with percutaneous repair but is associated with higher in-hospital morbidity and mortality; 3) successful surgical treatment of mitral PVLs in patients is feasible after failed percutaneous repair attempts; 4) repeat interventions were required in up to 15% of patients; and 5) after risk adjustment, there was no significant difference in short- or long-term mortality between the 2 treatment modalities.

Surgical repair or valve re-replacement is the historical gold standard treatment modality for severe symptomatic mitral PVL (American College of Cardiology/American Heart Association Class 1, Level of Evidence: B) (13). Percutaneous repair has emerged as an effective and alternative therapy for high-risk surgical candidates, with safety and efficacy demonstrated in multiple studies (9,10,14–17). Practice patterns and choice of procedure might differ among institutions on the basis of individual institutional

experience with complex percutaneous PVL repair and redo mitral valve surgery. Our study shows that at a tertiary referral center with an integrated team approach and extensive expertise in both procedures, the majority of patients are being treated using a percutaneous approach (**Figure 1**). These trend data are in line with several contemporary reports demonstrating the increasing interest in minimally invasive options to treat patients with severe PVLs (3,18–21).

In our study, surgical treatment of mitral PVLs was associated with more complete obliteration of the PVLs at the expense of higher rates of in-hospital mortality and complications compared with percutaneous repair. These findings deserve more scrutiny: First, patients' characteristics were distinctly different in the 2 groups; patients who underwent redo surgery were younger, had a higher prevalence of rheumatic heart disease, but also had a longer mean time between index valve surgery and treatment and a higher prevalence of chronic renal insufficiency and prior endocarditis. Patients who underwent percutaneous repair, in contrast, had a higher prevalence of atrial fibrillation, permanent pacemakers, and history of chest radiation and were more likely to be in New York Heart Association functional class III or IV heart failure at the time of the procedure. After risk adjustment, active endocarditis, chronic renal failure, and severe mitral annular calcifications were the only significant predictors of in-hospital mortality.

Second, the target of both procedures was the elimination of the mitral PVL. In the surgical group, PVL repair was possible in nearly one-half of the patients, but re-replacement of the valve was necessary in the other half. This approach achieved mild or less residual leak in 95% of patients. In the percutaneous group, successful crossing and deployment of repair device(s) across the leaks were achieved in 92% of patients, but reduction in PVLs to mild or less was possible in only 70%, despite the evolution of the percutaneous technique and outcomes over time. This could be related to the characteristics of the leaks in some patients (location, size, valve type, and so on) but also highlights the limitations of the currently available devices (17,20,22). The latter issue is particularly important. Despite the growing prevalence of PVL and the increasing use of percutaneous closure techniques, there are currently no devices that are specifically designed or approved for PVL repair in the United States. The AVP-II is the most commonly used off-label device because of its stability and low profile. However, many patients have crescentic or irregular shaped PVLs, and the AVP-II device may not be adequate for treatment of such defects. A new purpose-specific device, the Occlutech PLD Occluder (Occlutech, Jena, Germany), has been used with encouraging initial results in Europe (20). Unfortunately, this device is not available in the United States.

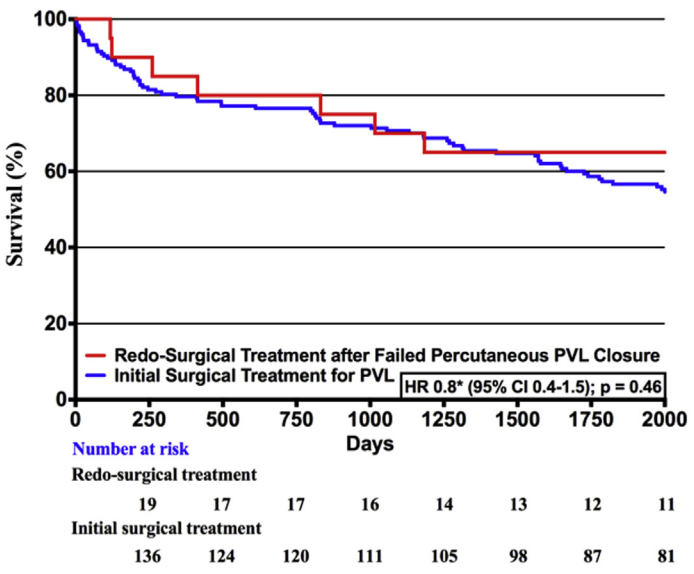
The decision to proceed to surgical versus percutaneous treatment was influenced by the invention and evolution of the percutaneous repair techniques in the past decade. On the basis of our integrated heart team experience, a suggested algorithmic approach to patients with significant mitral PVL is outlined in **Figure 5**. Key elements of the decision

TABLE 9 Multivariate Cox Regression for Predictors of All-Cause Mortality in Patients Undergoing Paravalvular Leak Closure

Statistical Method	Hazard Ratio	95% CI	p Value
Surgical closure of paravalvular leak	0.80	0.58–1.09	0.16
Age	1.02	1.01–1.04	0.002
Chronic obstructive pulmonary disease	1.55	1.07–2.24	0.02
Severe mitral annular calcification	1.60	1.17–2.17	0.003
Serum creatinine >1.5 mg/dl	1.65	1.25–2.19	<0.001
NYHA functional class III or IV congestive heart failure	1.97	1.39–2.78	<0.001
Active bacterial endocarditis	5.93	2.49–14.12	<0.001

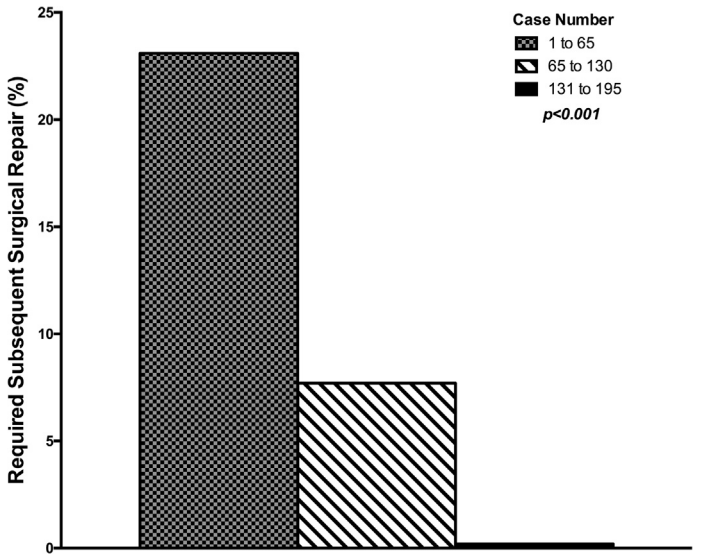
Abbreviations as in Table 7.

FIGURE 3 Outcomes of Surgical Intervention Following Failed Percutaneous Paravalvular Leak Closure



*Reference: initial surgical treatment; hazard ratio (HR) adjusted for age. CI = confidence interval; PVL = paravalvular leak.

FIGURE 4 Trends of Subsequent Surgery Treatment Following Percutaneous Paravalvular Leak Closure by Case Number Tertiles

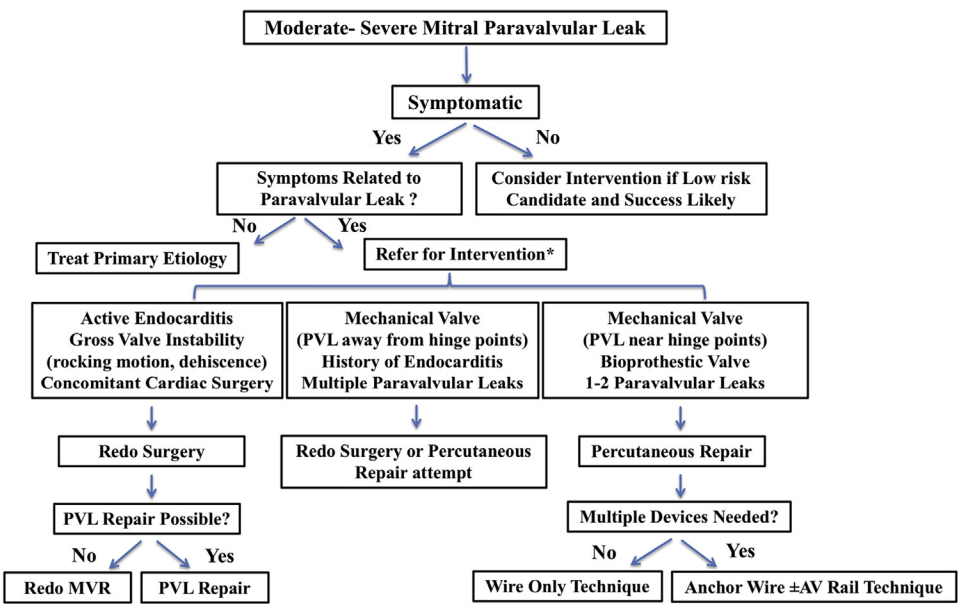


making in these patients are patient's age, comorbidities, presence of active endocarditis, rocking motion or dehiscence of the valve, location and number of PVLs, and the likelihood of successful percutaneous treatment. In minimally symptomatic patients, a strategy of careful observation must be weighed against early closure, and technical factors influencing success rates and procedural risk need to be weighed for individual patients.

The rates of repeat intervention during long-term follow-up were similar in the percutaneous and surgical groups (11.3% vs. 17.2%, respectively; p = 0.10). The mean time to repeat intervention, however, was significantly shorter in the percutaneous group (6.2 ± 7.4 months) compared with the surgical group (42.8 ± 43.8 months). This is possibly explained by the difference in the indications for repeat interventions in the 2 groups; the majority of repeat interventions in the percutaneous group were due to persistent residual leaks and/or severe hemolysis, whereas late recurrence of PVLs was the main indication for repeat interventions in the surgical group.

Finally, patients with symptomatic mitral PVLs constitute a high-risk cohort of patients with substantial long-term mortality (>50% at 5 years). This excess mortality seems to be similar following surgical and transcatheter treatment (adjusted hazard ratio: 0.8; 95% CI: 0.6 to 1.1; p = 0.16). These findings are analogous to previous reports suggesting a significant persistent mortality in patients with mitral PVLs even after PVL repair (7,23). It should be noted, however,

FIGURE 5 Treatment Algorithm for Patients With Mitral Paravalvular Leaks



*Refer to tertiary center if institutional experience in paravalvular leak treatment is limited. AV = arteriovenous; MVR = mitral valve replacement; PVL = paravalvular leak.

that patients who undergo mitral valve replacement have poor long-term survival overall. Two large institutional reports and a nationwide analysis of Medicare patients found 5-year mortality rates of 31% to 35% in patients who underwent mitral valve replacement (24–26). Further studies are needed to investigate the incidences, causes, and predictors of PVL so that preventive measure can be developed.

STUDY LIMITATIONS. First, the study was retrospective in nature. Second, there was potential for referral basis. Third, the ability to infer conclusions on the basis of group comparisons was severely limited because of the high degree of selection bias in our data. Nevertheless, the aim of this study was to describe the largest experience of an integrated team approach to the management of mitral PVL, and it can provide important insights into the heart team(s) involved in evaluating these complex patients.

Fourth, the data presented in this study are from a tertiary referral center with considerable experience in both percutaneous and surgical PVL treatment. These data should be interpreted with caution when applying these techniques at low-volume or emerging centers given the known learning curve of these complex procedures. In addition, the results of this study may not be generalizable to practices outside the United States because of the availability of purpose-specific devices outside the US.

Last, grading of mitral PVLs can be challenging. Echocardiographic measures used to grade PVLs are semiquantitative and suffer from limited validation. This could lead to interpretation variability, which may affect the results of this study.

CONCLUSIONS

The majority of mitral PVLs can be treated percutaneously. Surgical treatment of mitral PVLs achieves a higher degree of leak reduction but is associated with higher early morbidity and mortality compared with percutaneous repair. Effective management of these patients requires an integrated team approach that includes both percutaneous and surgical treatment and weighs early versus late treatment on the basis of clinical and anatomic factors.

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PERSPECTIVES

WHAT IS KNOWN? Percutaneous techniques have assumed a key role in the management of patients with severe symptomatic mitral PVLs.

WHAT IS NEW? Surgical treatment of mitral PVLs is associated with a higher degree of leak reduction compared with percutaneous treatment. Nevertheless, long-term survival is comparable for both treatment modalities.

WHAT IS NEXT? Patients with symptomatic mitral PVLs are best treated with an integrated team approach incorporating both surgical and percutaneous techniques.

REFERENCES

1. Genoni M, Franzen D, Vogt P, et al. Paravalvular leakage after mitral valve replacement: improved long-term survival with aggressive surgery? Eur J Cardiothorac Surg 2000;17:14–9.

2. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using transoesophageal echocardiography. Heart 2003;89:1316–21.

3. Hwang HY, Choi JW, Kim HK, Kim KH, Kim KB, Ahn H. Paravalvular leak after mitral valve replacement: 20-year follow-up. Ann Thorac Surg 2015;100:1347–52.

4. Cho IJ, Hong GR, Lee S, Byung-Chul C, Ha JW, Chung N. Predictors of prognosis in patients with mild to moderate paravalvular leakage after mitral valve replacement. J Card Surg 2014;29:149–54.

5. Bloch G, Vouhe PR, Menu P, et al. Long-term evaluation of bioprosthetic valves: 615 consecutive cases. Eur Heart J 1984;5 Suppl D:73–80.

6. Miller DL, Morris JJ, Schaff HV, Mullany CJ, Nishimura RA, Orszulak TA. Reoperation for aortic valve periprosthetic leakage: identification of patients at risk and results of operation. J Heart Valve Dis 1995;4:160–5.

7. Taramasso M, Maisano F, Denti P, et al. Surgical treatment of paravalvular leak: Long-term results in a single-center experience (up to 14 years). J Thorac Cardiovasc Surg 2015;149:1270–5.

8. Garcia-Borbolla Fernandez R, Sancho Jaldon M, Calle Perez G, et al. Percutaneous treatment of mitral valve periprosthetic leakage. An alternative to high-risk surgery? Rev Esp Cardiol (Engl Ed) 2009;62:438–41.

9. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circ Cardiovasc Interv 2011;4:314–21.

10. Ruiz CE, Jelnin V, Kronzon I, et al. Clinical outcomes in patients undergoing percutaneous closure of periprosthetic paravalvular leaks. J Am Coll Cardiol 2011;58:2210–7.

11. Eleid MF, Cabalka AK, Malouf JF, Sanon S, Hagler DJ, Rihal CS. Techniques and outcomes for the treatment of paravalvular leak. Circ Cardiovasc Interv 2015;8:e001945.

12. Ruiz CE, Hahn RT, Berrebi A, et al. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis: an expert statement. J Am Coll Cardiol 2017;69:2067–87.

13. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.

14. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Long-term follow-up of percutaneous repair of paravalvular prosthetic regurgitation. J Am Coll Cardiol 2011;58:2218–24.

15. Cruz-Gonzalez I, Rama-Merchan JC, Arribas-Jimenez A, et al. Paravalvular leak closure with the Amplatzer Vascular Plug III device: immediate and short-term results. Rev Esp Cardiol (Engl Ed) 2014;67:608–14.

16. Sanchez-Recalde A, Moreno R, Galeote G, et al. Immediate and mid-term clinical course after percutaneous closure of paravalvular leakage. Rev Esp Cardiol (Engl Ed) 2014;67:615–23.

17. Nietlispach F, Johnson M, Moss RR, et al. Transcatheter closure of paravalvular defects using a purpose-specific occluder. J Am Coll Cardiol Intv 2010;3:759–65.

18. Calvert PA, Northridge DB, Malik IS, et al. Percutaneous device closure of paravalvular leak: combined experience from the United Kingdom and Ireland. Circulation 2016;134:934–44.

19. Garcia E, Arzamendi D, Jimenez-Quevedo P, et al. Outcomes and predictors of success and complications for paravalvular leak closure. An analysis of the Spanish Real-World Paravalvular Leaks Closure Registry (HOLE registry). EuroIntervention 2017;12:1962–8.

20. Goktekin O, Vatankulu MA, Ozhan H, et al. Early experience of percutaneous paravalvular leak closure using a novel Occlutech occluder. EuroIntervention 2016;11:1195–200.

21. Bouhout I, Mazine A, Ghoneim A, et al. Long-term results after surgical treatment of paravalvular leak in the aortic and mitral position. J Thorac Cardiovasc Surg 2016;151:1260–6.

22. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. The learning curve in percutaneous repair of paravalvular prosthetic regurgitation: an analysis of 200 cases. J Am Coll Cardiol Intv 2014;7:521–9.

23. Taramasso M, Maisano F, Pozzoli A, Alfieri O, Meier B, Nietlispach F. Catheter-based treatment of paravalvular leaks. EuroIntervention 2016;12 Suppl X:X55–60.

24. Vassileva CM, Mishkel G, McNeely C, et al. Long-term survival of patients undergoing mitral valve repair and replacement: a longitudinal analysis of Medicare fee-for-service beneficiaries. Circulation 2013;127:1870–6.

25. Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. Circulation 2001;104:I1–7.

26. Thourani VH, Weintraub WS, Guyton RA, et al. Outcomes and long-term survival for patients undergoing mitral valve repair versus replacement: effect of age and concomitant coronary artery bypass grafting. Circulation 2003;108:298–304.

KEY WORDS mitral valve, mitral valve re-replacement, paravalvular leak, patch repair, percutaneous closure

APPENDIX For a supplemental table and figures, please see the online version of this paper.

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