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ORIGINAL ARTICLE

Feasibility of transcatheter prosthetic paravalvular leakage closure: a single-center, exploratory safety evaluation study of transcatheter closure of prosthetic paravalvular regurgitation in Japan (STOP PARA study)

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Abstract

Objective The standard treatment of prosthetic paravalvular leakage (PVL) accompanied by heart failure or hemolytic anemia is repeat open surgery. Although favorable outcomes for transcatheter prosthetic PVL closure in patients with a high surgical risk for repeat open surgery have been reported, procedural feasibility has not been examined in Japan.

Methods From March 2015 to November 2015, transcatheter PVL closure in mitral position was performed in four patients (age range 41–78, three females) with high surgical risk due to history of repeated surgeries, chest radiation and reconstruction of the mitral annulus after debridement of abscess owing to infective endocarditis. All procedures were performed via a transapical approach under general anesthesia.

Results Of four patients, the indications for PVL closure of two patients were heart failure, and those of the others were hemolytic anemia. There were no major complications, mortalities, or prolonged intensive care unit or hospital stays. Technical success was achieved in two patients. Moderate paravalvular regurgitation persisted in one patient, although regurgitation reduction of one grade was obtained. In one patient, occluder devices were not deployed because the wire could not cross the defect. Improvement in New York Heart Association functional class compared with that at baseline was observed in two patients.

Conclusions The safety and acute technical success rates of transcatheter mitral PVL closure via a transapical approach were confirmed in Japanese patients. In Japan, transcatheter PVL closure may be an alternative option for patients with PVL who have a high surgical risk.

Keywords Prosthetic paravalvular leakage · Transcatheter closure · Transapical approach · Multimodality imaging

Introduction

Prosthetic paravalvular leakage (PVL) refers to the condition of regurgitation through the region adjacent to a prosthetic valve, without prosthetic valve failure. The incidence of PVL after surgical valve replacement is 2–10% in the aortic position and 7–17% in the mitral position. Most patients with PVL do not exhibit symptoms; however, 1–5% exhibit clinically serious symptoms such as congestive heart failure or hemolytic anemia refractory to medical therapy [1–3]. Conservative treatment for clinically severe regurgitation results in 10-year survival rates of approximately 30% [4]. Therefore, symptomatic patients are referred for repeat valve surgery, despite having a high operative mortality of 6–42%

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(including 13%, 15%, and 37% for second, third, and fourth surgery, respectively) [5, 6].

Percutaneous approaches for PVL treatment have been recently developed. These approaches can be performed with relatively high rates of procedural success (77–86%) and an acceptable incidence of complications (mortality rate was 1.7–1.8%) for patients unable to undergo surgery because of high operative risk [7–11]. Consequently, the guideline in the USA recommends transcatheter PVL closure for class IIa patients with a high surgical risk [12]. However, the feasibility of this alternative treatment is poorly evaluated in Japan.

Thus, we examined the acute and 30-day outcomes of patients who underwent transcatheter PVL closure in a Japanese hospital specializing in heart diseases.

Patients and methods

Study design

This was a prospective, single-center, exploratory safety evaluation Study of Transcatheter clOsure of Prosthetic PARAvalvular regurgitation (STOP PARA) to evaluate the feasibility and safety of transcatheter PVL closure for patients with heart failure and/or hemolytic anemia caused by PVL after heart valve replacement at the National Cerebral and Cardiovascular Center in Osaka, Japan. The Institutional Research Board of the National Cerebral and Cardiovascular Center approved this study. All patients or health-care surrogates provided written informed consent for all study-related procedures. This study was registered in the University Hospital Medial Information Network Clinical Trials Registry, with the identifier UMIN000021427.

Patient selection

Patients were considered for transcatheter closure if the following criteria were fulfilled: (1) aged > 20 years, (2) with more than mild paravalvular regurgitation, (3) with heart failure or hemolytic anemia that are resistant to medical treatments, and (4) having high operative risk or consensus among cardiologists and cardiac surgeons that conventional surgery would be associated with excessive morbidity and mortality. Clinically significant anemia was defined as hemoglobin levels of < 10 g/dL, which required repeated transfusion. In addition, hemolysis was identified by filling two of the four following criteria: serum lactate dehydrogenase level of > 460 U/L, blood hemoglobin level of < 13.8 g/dL for males or < 12.4 g/dL for females, serum haptoglobin levels of < 50 mg/dL, and reticulocyte count of > 2%. High operative risk was defined as expected mortality of > 8.0% estimated by Society of Thoracic Surgeons score [13], and/or the following risk factors were considered inoperative (at the discretion of the surgeons): porcelain aorta, mobile atherosclerosis at the aorta, history of mediastinal radiotherapy or mediastinitis, aged > 75 years with a left ventricular ejection fraction of < 40%, previous coronary artery bypass grafting, history of two or more cardiac surgeries, or liver cirrhosis.

Evaluation of PVL

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed for all study patients to evaluate the severity of regurgitation and the location, size, and shape of PVL (iE 33 or EPIQ 7; Philips Medical Systems, Best, The Netherlands). The severity of regurgitation was graded using a semiquantitative method using color Doppler TEE [14]. We determined PVL location using a modified clock-face system in the surgical view [8]. For the mitral position, the site between the clock-face position of 10 and 2 corresponds to the anterior part; between 2 and 6 corresponds to the posterolateral part; and between 6 and 10 corresponds to the posteroseptal part. Pre-procedural ECG-gated, multidetector computed tomography (MDCT) was performed for all patients within 3 months prior to the procedure (Somatom Definition Flash, Siemens Healthcare, Erlangen, Germany). All MDCT images were analyzed using the MDCT 3D workstation (Ziostation2, Ziosoft, Inc. Tokyo, Japan). All patients underwent cardiac catheterization to assess coronary artery stenosis and hemodynamic conditions prior to the procedure.

Procedure

All the procedures were performed by our heart team consisting of cardiovascular surgeons, cardiologists, and anesthesiologists. In a hybrid operating room at our institute, the patients were placed in a supine position under general anesthesia with fluoroscopic and TEE guidance. Referring to the pre-procedural enhanced CT, a small left anterior thoracotomy was performed at the appropriate position for apical puncture; usually the fifth intercostal space was selected. A short 6-Fr sheath was inserted into the left ventricle by direct visualization in combination with epicardial echocardiography assessment. A 0.035-in. Terumo wire was used to cross the mitral paravalvular defect in a retrograde fashion, directed by the sheath. After crossing the defect, the sheath was advanced across the defect, and two other guide wires were inserted through the sheath to allow an additional device to be deployed adjacent and in series to the implanted device, if necessary. The sheath was removed and inserted into one of the three guidewires. In the present study, the Amplatzer Vascular Plug II (St. Jude Medical, St. Paul, MN, USA), a self-expandable nitinol wire-mesh device, was selected as the occluder device. It can easily

be delivered through the sheath and across the paravalvular defects owing to its low profile and high flexibility. It was commercially available in Japan; however, only for off-label use. If substantial residual regurgitation was observed, an additional device was deployed into the defects using the remaining guidewire.

After the procedure, the patients were instructed to take 100 mg aspirin daily for 180 days. For the patients with known or suspected aspirin contraindications, other antiplatelet or anticoagulant therapies were suggested.

Follow-up

TEE was performed 1 week after the procedure. TTE was performed 1 week and 1 month after the procedure. We estimated functional capacity according to New York Heart Association (NYHA) functional class and the 6-min walk test. The 6-min walk test was performed at baseline and 1 week after the procedure. Laboratory tests were performed at baseline, 1 week, and 1 month after the procedure.

Evaluation of feasibility and safety of the procedure

The primary end points of this study were intraoperative safety and technical success rate. Intraoperative safety was defined as no major complications, including death from any cause, symptomatic stroke, myocardial infarction, cardiac rupture/tamponade, cardiogenic shock, prosthetic valve dysfunction, life-threatening bleeding, major vessel injury, embolism, and/or device malpositioning. Technical success was defined as successful deployment of one or more occluder devices, which significantly reduced paravalvular regurgitation to mild or less residual regurgitation after the procedure, as evaluated using TEE. Secondary end points were improvement of symptoms owing to heart failure or hemolytic anemia. Improvement in symptoms was defined as follows: improvement (compared with baseline) in NYHA functional class ≥ 1 or improvement in the 6-min walk test of ≥ 25 m compared with that at baseline.

Results

Patients' characteristics

Four patients were enrolled in this study; the indications for PVL closure were heart failure ($n=2$) and hemolytic anemia ($n=2$; Table 1). Three patients underwent ≥ 2 prior thoracotomies. In addition, case 2 had a history of chest radiation for breast cancer, and case 4 had a history of reconstruction of the mitral annulus after debridement of a valve ring abscess owing to infective endocarditis. TEE indicated greater than moderate regurgitation in all patients. In addition, MDCT confirmed the location of PVL and clearly demonstrated the shape and size of PVL in all patients. All patients had mitral PVLs, and multiple PVLs were observed in two patients.

Procedure results

No major complications were observed in any of the four cases (Table 2). Technical success was obtained in two cases (50%). In one case (25%), occluder devices were not deployed because the wire could not pass through the defect. Moderate paravalvular regurgitation persisted in one case (25%) after the procedure. Although one patient (25%) had a wound infection after the procedure, it resolved following an antibiotic therapy.

In case 1, one device was successfully implanted at the appropriate site, and regurgitation was significantly reduced (Fig. 1). However, hemolysis developed after the procedure. It is likely this occurred because of flow acceleration through the residual narrow space beside the implanted device. In case 2, two devices were successfully implanted at the PVL site with residual PVL leakage. We attempted to deploy another device to close the residual leakage but failed owing to the impingement of the Bjork–Shiley tilting disk valve at deployment. In case 3, we could not cross the small posteroseptal PVL with a guidewire (Fig. 2). In case 4, two devices were successfully implanted at PVL, and the regurgitation was significantly reduced. However, moderate regurgitation beside the closure device persisted. We attempted to cross the wire through the residual PVL beside the closure device, but were unsuccessful. Retrospective analyses of MDCT demonstrated the irregular shape of the entry orifice from LV with the wide and narrow paths. Considering the site of residual paravalvular regurgitation, we speculated that two closure devices were implanted at the wide path, but any device would not pass the narrow path.

Follow-up at 1 week and 1 month after the procedure

Reduction of regurgitation to no greater than mild regurgitation just after the procedure in two patients persisted during TEE assessments at 1 week after the procedure and at 1 month after the procedure. No worsening of PVLs, compared with baseline, was observed in any patient, regardless of the procedural results. Improvement, compared with baseline, in NYHA functional class and 6-min walk test was observed in two patients whose indications for PVL closure were heart failure, rather than hemolysis (Fig. 3). All patients, including the patient who could not tolerate any closure device (case 3), visited an outpatient clinic on foot at 1 month

Table 1 Patients' characteristics before the procedure

	Case 1	Case 2	Case 3	Case 4
Age (years)	72	68	78	41
Sex	Male	Female	Female	Female
STS score (%)	9.7	7.9	5.9	2.7
Limited lung disease	Yes	No	No	No
Coronary artery disease	No	No	No	No
Cerebrovascular disease	No	No	No	No
Peripheral vascular disease	No	No	No	No
eGFR (60 mL/min/1.73 m^2)	No	Yes	Yes	No
Pulmonary hypertension	Yes	Yes	No	No
Number of prior thoracotomy	3	4	1	2
Chest radiation	No	No	Yes	No
Porcelain aorta	No	No	No	No
Severe immobility	No	No	No	No
Valve diseases at the first thoracotomy	Rheumatic	Rheumatic	Rheumatic	Infective endocarditis
Indication of prosthetic valve repair				
Heart failure	Yes	No	No	Yes
Hemolytic anemia	No	Yes	Yes	No
Six-minute walk (m)	310	350	295	480
NYHA	3	2	2	2
Hemoglobin (g/dL)	11.0	10.9	10.5	11.9
Total protein (g/dL)	8.5	7.4	7.0	7.0
Albumin (g/dL)	4.2	4.4	4.1	4.3
Total bilirubin (mg/dL)	0.9	1.8	1.3	1.4
Indirect bilirubin (mg/dL)	0.4	1.3	0.9	1.0
LDH (U/L)	679	1064	1053	494
eGFR (mL/min/1.73 m^2)	63.0	36.0	51.0	64.8
BNP (pg/mL)	40.4	67.5	234.9	109.8
Transthoracic echocardiography				
LV diastolic dimension (mm)	47	45	40	47
LV systolic dimension (mm)	33	28	28	28
LV ejection fraction (%)	57	60	60	66
LA dimension (mm)	53	34	43	40
Aortic regurgitation	None	Mild	None	None
Mitral regurgitation	Moderate	Moderate	Mild	Severe
Tricuspid regurgitation	Moderate	Moderate	Mild	Mild
Transesophageal echocardiography				
Aortic regurgitation	None	None	None	None
Mitral regurgitation	Severe	Moderate	Moderate	Severe
Position of PVL	A	PS/PL	PL	PS/A
Right heart catheterization				
Mean PCWP (v-wave) (mmHg)	22 (37)	18 (32)	16 (29)	16 (28)
Mean PAP (mmHg)	42	33	26	23
Mean RAP (mmHg)	7	6	15	6
Cardiac index (L/min/m^2)	2.66	2.05	1.92	2.56
PVR (dyn s/cm^5)	1506	1858	1926	1721
SVR (dyn s/cm^5)	407	472	229	170

A anterior, *BNP* brain natriuretic peptide, *eGFR* estimated glomerular filtration rate, *LA* left atrial, *LV* left ventricular, *LDH* lactase dehydrogenase, *NYHA* New York Heart Association, *PAP* pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *PL* posterolateral, *PS* posteroseptal, *PVL* paravalvular leakage, *PVR* pulmonary vascular resistance, *RAP* right arterial pressure, *STS* Society of Thoracic Surgeons, *SVR* systemic vascular resistance

Table 2 Procedure characteristics

	Case 1	Case 2	Case 3	Case 4
Status of valves				
Mitral valve	ATS 25 mm	BS 29 mm	SJM 29 mm	SJM 27 mm
Aortic valve	ATSAP 18 mm	ATSAP 20 mm	SJM 21 mm	Native
Tricuspid valve	Annular plasty	Annular plasty	Annular plasty	Native
Number of devices implanted	1	2	0	2
Positions of device implanted	A	PL*2	NA	PS*2
Size of AVP II	8 mm	8 mm/8 mm	NA	10 mm/10 mm
Operation time (min)	248	357	285	201
Procedure time (min)	131	237	170	117
Fluoroscopy time (min)	28	68	62	58
Residual regurgitation from PVL				
Grade	Mild	Mild	Moderate	Moderate
Position of residual PVL	A	PS	PL	PS/A
Technical success	Yes	Yes	No	No
Intensive care unit stays (days)	3	4	3	3
Hospital stays (days)	13	10	14	10

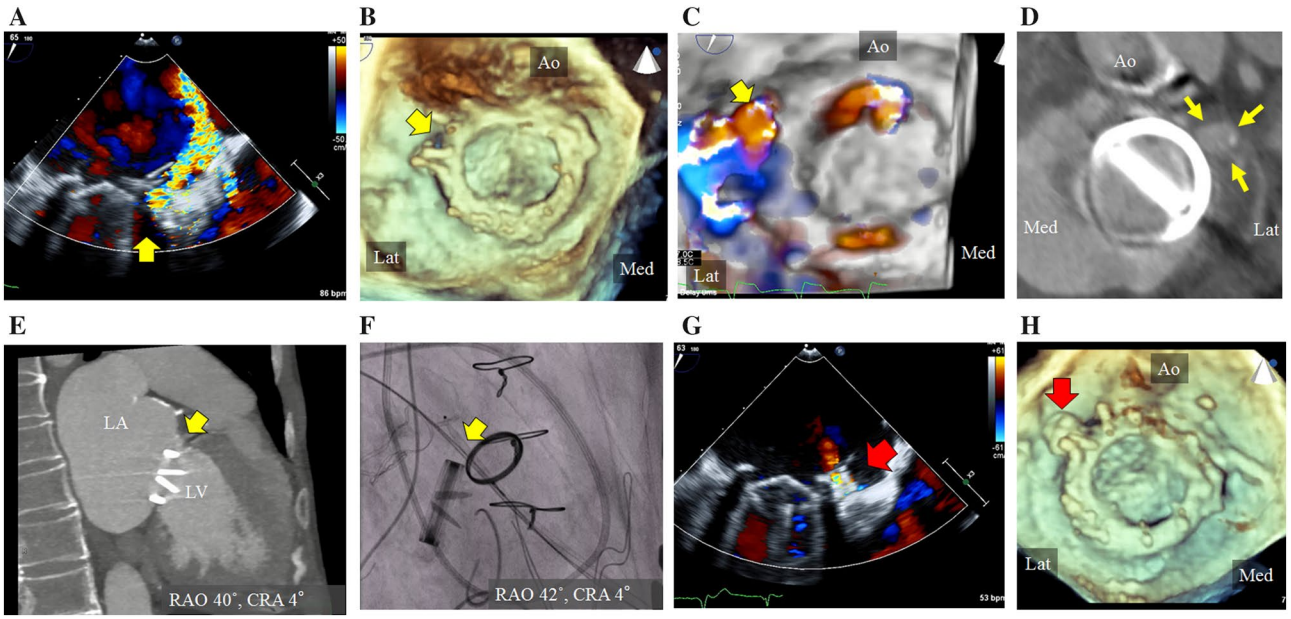

Fig. 1 Pre-procedural evaluation of PVL using transesophageal echocardiography and multidetector CT in case 1. Real-time 3D transesophageal echocardiography indicated that PVL was located at the anterolateral position, as indicated by yellow arrows (**a**–**c**). From short-axis (**d**) and long-axis (**e**) CT images, the shape of the defect appeared round and cylindrical, and the size of PVL was 5.5 and 6 mm in the short-axis image. Pre-procedural estimation of optimal angulation of C-arm helps deliver the wire and catheter and shorten the fluoroscopy time (**e, f**). We successfully implanted a closure device at the site, which are indicated by the red arrows in **g, h**. *Ao* ascending aorta, *CRA* cranial, *LA* left atrium, *LV* left ventricle, *Lat* lateral side, *Med* medial side, *RAO* right anterior oblique

after the procedure. Regarding hemolysis, one patient with hemolysis before the procedure (case 2) experienced remission at 1 month after the procedure, whereas one patient (case 1) exhibited worsening of hemolysis at 1 month after the procedure (Fig. 3).

Discussion

This study demonstrates the feasibility of transcatheter mitral PVL closure via a transapical approach in Japanese patients.

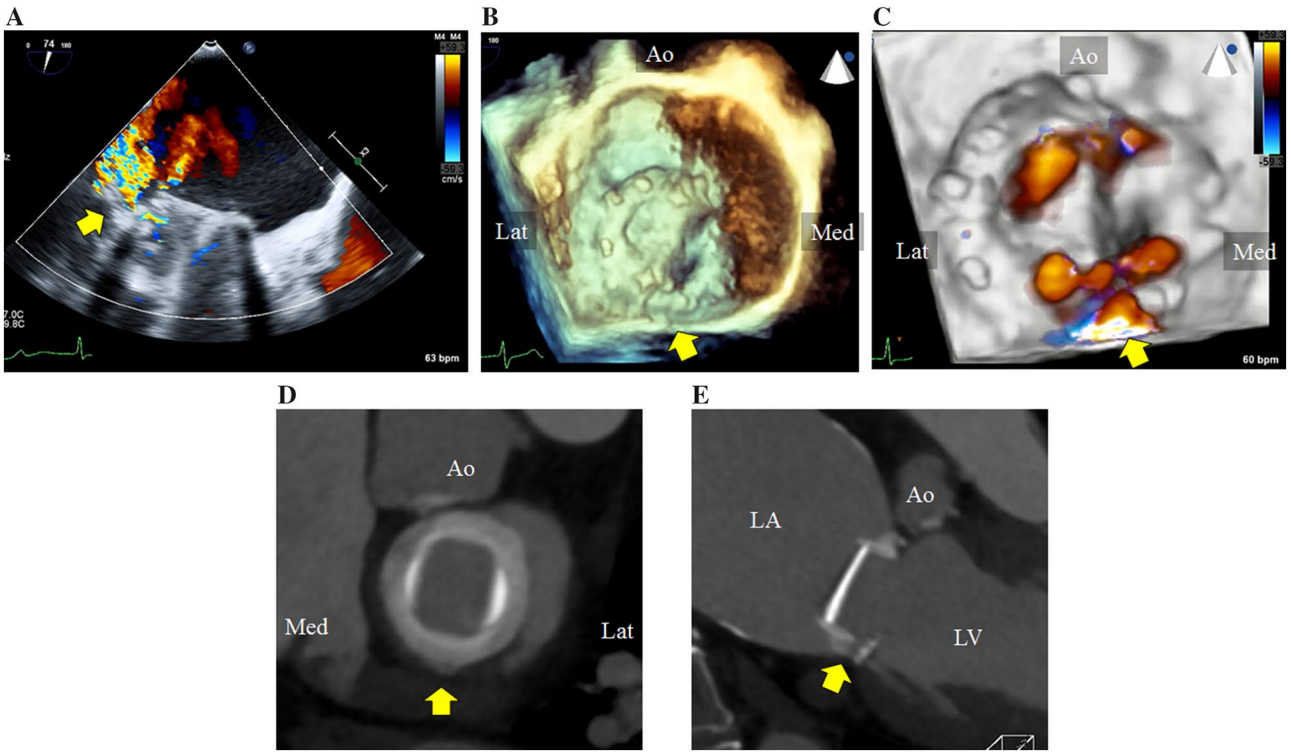

Fig. 2 Small and tortuous path of PVL with hemolysis in case 3. A small PVL was observed at the inferoposterior position with moderate mitral regurgitation, as indicated by yellow arrows (**a–c**). The CT image indicated round and tortuous shape of PVL with a diameter of 2 mm (**d, e**), indicating that it was not easy to cross the defect. The wire would not pass through the defect. *LAA* left atrial appendage, other abbreviations as in Fig. 1

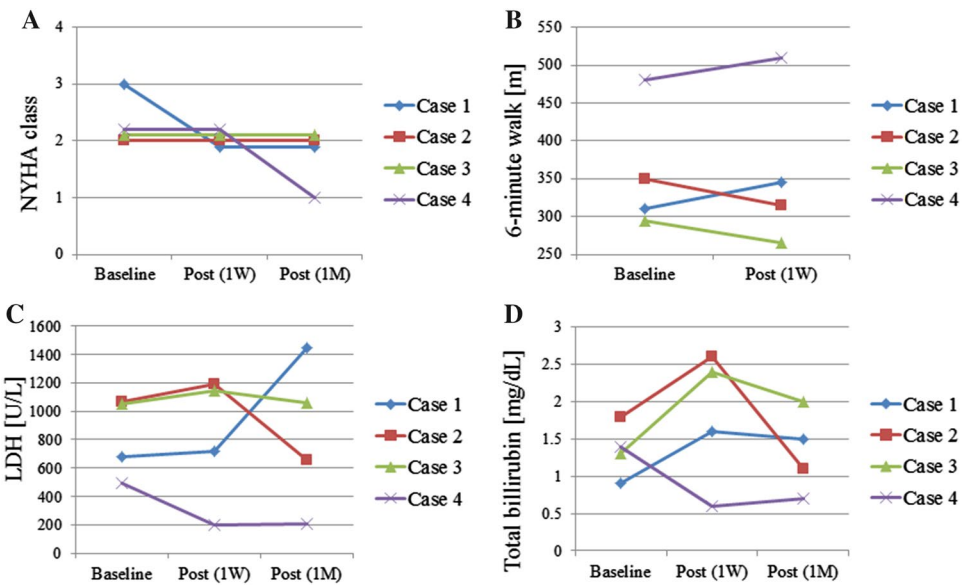

Fig. 3 Transition of indices regarding functional status and hemolysis. Improvement (compared with baseline) in NYHA functional class and 6-min walk was observed in two patients whose indication of PVL closure was heart failure rather than hemolysis. Regarding hemolysis, one patient with hemolysis before the procedure (case 2) had remission at 1 month after the procedure, whereas one patient (case 1) had worsening of hemolysis at 1 month after the procedure. *1W* 1 week after the procedure, *1M* 1 month after the procedure

Transcatheter PVL closure was recently developed, and comfortable outcomes have been reported in patients with a high surgical risk [7–11]. In Japan, there are few case reports regarding transcatheter PVL closure via transseptal and transapical approaches [15, 16]. In this study, we confirmed that transcatheter PVL closure via a transapical approach could be safely performed in four patients with a high surgical risk. Our results are consistent with those of previous studies reported in Europe and the USA [8, 9]. In this study, no patients experienced life-threatening

complications, which is the priority issue to accumulate the experiences of those advanced procedure. Furthermore, assuming standard repeat surgery results in difficulties during perioperative management, it should be noted that the lengths of intensive care unit stays and hospital stays were relatively brief, regardless of the technical results of PVL closure.

Based on our four procedural understanding, we identified the following issues that may improve the clinical success rate of the transcatheter PVL closure: (1) predicting the difficulty associated with crossing the wire and catheter into the defect and (2) the appropriate selection of the closure device type and size.

The PVL length and shape vary owing to various available suture techniques for valve replacement and postoperative scar formation. In other words, the path of PVL could be thin and tortuous, and its axis is infrequently perpendicular to the annular plane of the prosthetic valve. Additionally, flow disturbance and high shear stress through the PVL may cause hemolysis, indicating a thin and tortuous PVL path [17]. Considering the mechanisms of PVL-triggered hemolysis, the path of PVL associated with hemolytic anemia is expected to be complex and hard to cross device systems into the PVL defect. Therefore, a preprocedural assessment of PVL is essential for achieving procedural success. Considering the mechanisms of PVL-triggered hemolysis and our experience of 4 cases, the following items might indicate favorable procedural and clinical success of transcatheter PVL closure: straight and not too thin path of PVL defect and heart failure mainly due to severe regurgitation. On the contrary, the following items might not indicate favorable outcomes: thin and/or tortuous path of PVL defect and heart failure mainly due to hemolytic anemia. An ECG-gated MDCT could help visualize the paths and forms of PVLs and might imply the clinical outcomes after the transcatheter PVL closure.

An appropriate selection of the closure device type and size is crucial to prevent the migration, embolization, and fracture of the closure device and the worsening of hemolytic anemia owing to residual leakage. New-onset hemolytic anemia occurred in 10% of the patients after transcatheter PVL closure [18]. Considering that the PVL-originating hemolytic anemia is associated with poor outcomes [10, 19], residual and/or new-onset hemolytic anemia due to PVL should be prevented. MDCT with high spatial resolution could assist in the selection of an optimal closure device. Additionally, specialized new devices such as the Occlutech Paravalvular Leak Device (Occlutech, Jena, Germany) might solve the issues associated with the mismatch between the PVL defects and devices. The Occlutech devices have two types of designs of frames (rectangular or square) and two types of connections between the discs (thick or thin). The diversity of the occuluder devices enables optimal device selection for variable shapes and sizes of PVL defects.

Our study has several limitations. First, because in this study acute and 30-day outcomes were examined to evaluate the safety and technical success rates of transcatheter PVL closure, the long-term durability of the closure device after this procedure could not be assessed. Second, all procedures in this study were performed within a time period of early investigator learning. Therefore, increased experiences with this procedure could improve the technical and clinical success rates in the future. Additionally, because we assumed that the transcatheter PVL closure itself did not increase the risk for future repeat open heart operations, performing this procedure could be an initial feasible option for patients with a high surgical risk at heart valve centers of experienced surgeons and cardiologists.

Conclusions

We confirmed the safety and technical success rates of transcatheter mitral PVL closure via a transapical approach in Japanese patients with a high surgical risk. The assessment of anatomical characteristics by multiple modalities could help in improving the technical and clinical success rates so that patients with a lower surgical risk could benefit from transcatheter PVL closure.

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Compliance with ethical standards

Conflict of interest The authors report no conflicts of interest.

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