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STRUCTURAL

Transcatheter Mitral Valve Implantation Using the HighLife System

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ABSTRACT

OBJECTIVES This study is the first report of 2 cases of HighLife (HighLife, Paris, France) implantation in humans.

BACKGROUND Transcatheter mitral valve implantation represents a promising approach to treating mitral regurgitation in patients at increased risk of perioperative mortality. The HighLife transcatheter mitral valve is a 2-component system. The valve is implanted in the mitral position and is anchored by interacting and then reaching an equilibrium position with a previously positioned subannular implant.

METHODS The procedures were successfully performed in a 69-year-old man and a 65-year-old woman with severe functional mitral regurgitation. Both patients were in New York Heart Association functional class IV heart failure with depressed left ventricular ejection fraction and additional comorbidities.

RESULTS The valve was implanted uneventfully in both patients. General anesthesia was used. The subannular implant was deployed through the transfemoral access, whereas the transcatheter mitral valve was released using the transapical access. Patients maintained hemodynamically stable. There were no intraoperative complications. Acutely, post-procedural echocardiograms demonstrated excellent prosthetic valve function with a low transvalvular gradient and no paravalvular leak and left ventricular outflow tract obstruction. Both patients had mild intraprosthetic regurgitation. Patient #1 survived at 5-months follow-up in New York Heart Association functional class II with excellent prosthesis performance. Patient #2 expired 4 days after a technically successful procedure, because the left ventricle did not tolerate the reduction of mitral regurgitation and despite a high dose of inotropic agents the left ventricular function rapidly deteriorated.

CONCLUSIONS Transcatheter mitral valve implantation using the 2-component HighLife system is technically feasible and can be performed safely. Early hemodynamic performance of the prosthesis was excellent. (J Am Coll Cardiol Intv 2017;10:1662–70) © 2017 by the American College of Cardiology Foundation.

Transcatheter mitral valve implantation (TMVI) represents a promising approach to treating mitral regurgitation (MR) in patients at increased risk of perioperative mortality (1). To date, several transcatheter mitral valve systems are under preclinical and clinical investigation (1–5). Each of them carries specific features that have the goal to ensure a predictable delivery and

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an efficient anchoring and sealing to the mitral annulus, while preserving surrounding cardiac structures and the patency of the left ventricle outflow tract (LVOT). The HighLife transcatheter mitral valve system (HighLife, Paris, France) is a 2-component system (6). The design of the valve with implantation of the prosthesis in a previously positioned subannular implant (SAI) is intended to seal without paravalvular leakage and prevent LVOT obstruction. This device has already been tested in acute and chronic animals with promising outcomes (data not published). No human cases have been described in the published data. The present study is the first report of 2 cases of HighLife implantation in humans.

TMVI DEVICE OVERVIEW

The HighLife TMVI technology has been described previously (**Figure 1**) (6). Briefly, the device, which is currently available only in 1 size, is composed of 2 separate components. The valve consists of a nitinol alloy-based, self-expanding frame, covered with a polyester graft and trileaflet bovine pericardium. The frame shape has a pre-formed groove in the annular region so as to create an interference with the loosely placed SAI. The SAI is a polymer tube, covered with a polyester graft with a nitinol hook that allows for the creation of a ring with a single definite length (31 mm). The SAI comprises 2 distal ends mounted on each side of the guidewire loop surrounding the native mitral valve. The first end is tapered with a nitinol clip. The second end has a flared shape designed to host the nitinol clip. When the open ring is pushed forward on the guidewire loop, the 2 ends are brought together until the clip engages the opposite end and closes the ring. The valve is loaded into a 39-F catheter delivery system that is currently introduced through the apical access, whereas the SAI is placed using an 18-F catheter compatible SAI delivery catheter (SDC) that is inserted through the femoral artery and advanced retrogradely into the left ventricle (LV) after having crossed the aortic valve. The SDC is mounted on a guidewire loop encircling the native mitral valve apparatus. This loop is placed in a previous step using a dedicated 18-F catheter loop placement catheter (LPC). The LPC includes 3 components: 1 tube that ends with the nose cone, and 2 sets of tubes (on each side there is an intermediate tube with a 90° hosting a smaller subannular tube that extends into the subannular groove) for the guidewire and the snare, respectively. The interaction between the 2 components (prosthesis and SAI) that "jail" the mitral leaflets confers to the system a stable position and sealing within the mitral valve.

PRE-OPERATIVE ASSESSMENTS

Permission to proceed with transcatheter mitral valve replacement by using the HighLife transcatheter mitral valve system was granted on compassionate grounds by the Italian Ministry of Health and the local ethical committee. Both patients signed dedicated informed consent forms.

Cardiac-gated multislice computed tomography imaging was performed to assess mitral valve apparatus and aortomitral angle, and facilitate the pre-operative planning of fluoroscopic implant angles. Multislice computed tomography examinations were performed using a 64-slice Discovery HD 750 high-definition or volume computed tomography scanner (GE Healthcare, Milwaukee, Wisconsin). Multislice computed tomography data were reconstructed in 10% intervals throughout the cardiac cycle with a section thickness of 0.6 mm and an increment of 0.4 mm using a medium soft-tissue convolution kernel. All data sets were transferred to a dedicated post-processing workstation equipped with FluoroCT 3.0. For mitral annular assessment, mid- to late-diastolic image reconstructions were identified. Specifically, atrial dimensions on 85% to 95% reconstructions were assessed, depending on the presence of atrial contraction with the goal of evaluating the annulus on the last reconstruction before the atrial contraction. Using the late-diastolic reconstructions, the mitral annulus was tracked as previously reported (**Figure 2**) (7).

Patency of the LVOT was assessed both in late diastolic and late systolic images by simulating hypothetical TMVI with the device deployed in the mitral annulus (**Figure 3**). Finally, along the course of the subannular space, all the false chordae tendineae were identified and highlighted with a marker. This step was critical because the loop must be placed excluding the subannular fibrous or fibromuscular structures. Indeed, the entrapment of the SAI in 1 or more basal cords might determine a suboptimal anchoring and sealing of the transcatheter mitral valve.

CASE DESCRIPTIONS

PATIENT #1. Patient #1 (**Table 1**) was a 69-year-old man with previous myocardial infarction and

ABBREVIATIONS AND ACRONYMS

LPC = loop placement catheter

LV = left ventricle

LVOT = left ventricle outflow tract

MR = mitral regurgitation

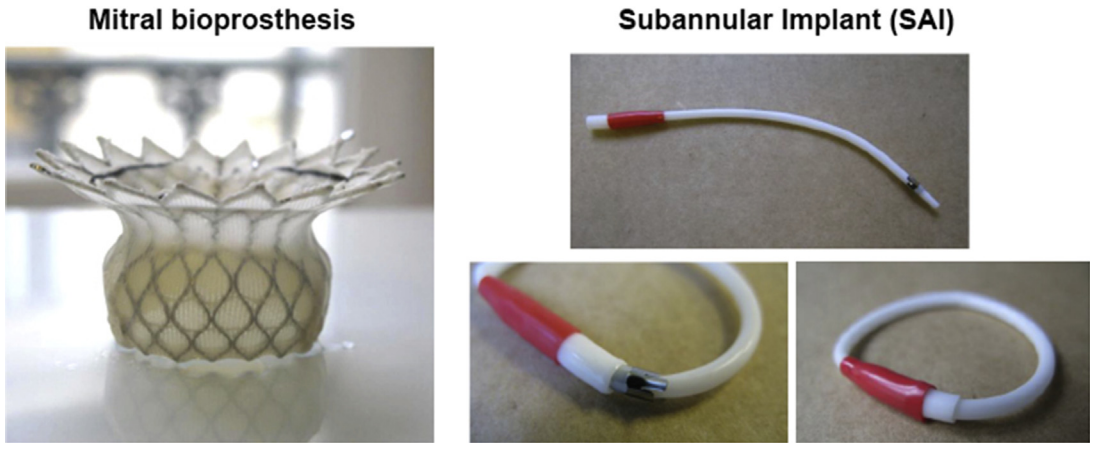
SAI = subannular implant

SDC = subannular implant delivery catheter

TEE = transesophageal echocardiography

TMVI = transcatheter mitral valve implantation

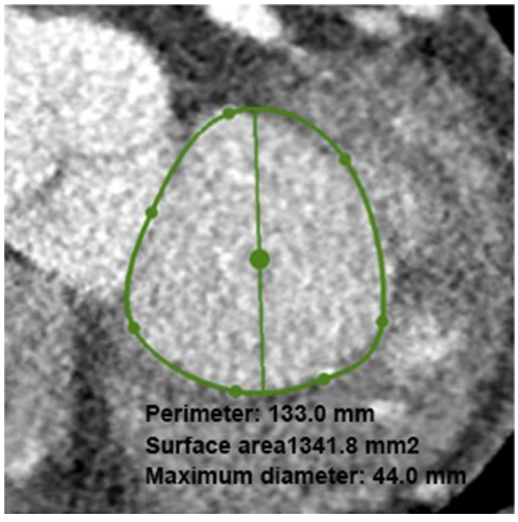
FIGURE 1 Transcatheter Mitral Valve Prosthesis and Subannular Implant



Images of transcatheter mitral valve prosthesis and subannular implant.

coronary artery bypass grafting who developed severe ischemic cardiomyopathy and functional MR. He has had multiple previous in-hospital admissions for heart failure despite optimal medical therapy. An echocardiogram documented severe LV dysfunction (ejection fraction, 25%) and dilation. LV end-diasystolic diameter was 76 mm, and estimated pulmonary arterial systolic pressure was 60 mm Hg. There was severe functional MR with tethering of both anterior and posterior leaflets. An accessory membrane lying perpendicular to the interatrial septum was also observed. This anatomic feature prevented us to propose the patient for transseptal-based approaches for transcatheter mitral valve repair, such as MitraClip (Abbott Vascular, Abbott Park, Illinois) and CardioBand (Valtech Cardio, Or Yehuda, Israel) procedures. The calculated logistic EuroScore 2 risk of mortality for mitral valve replacement was 8.9%.

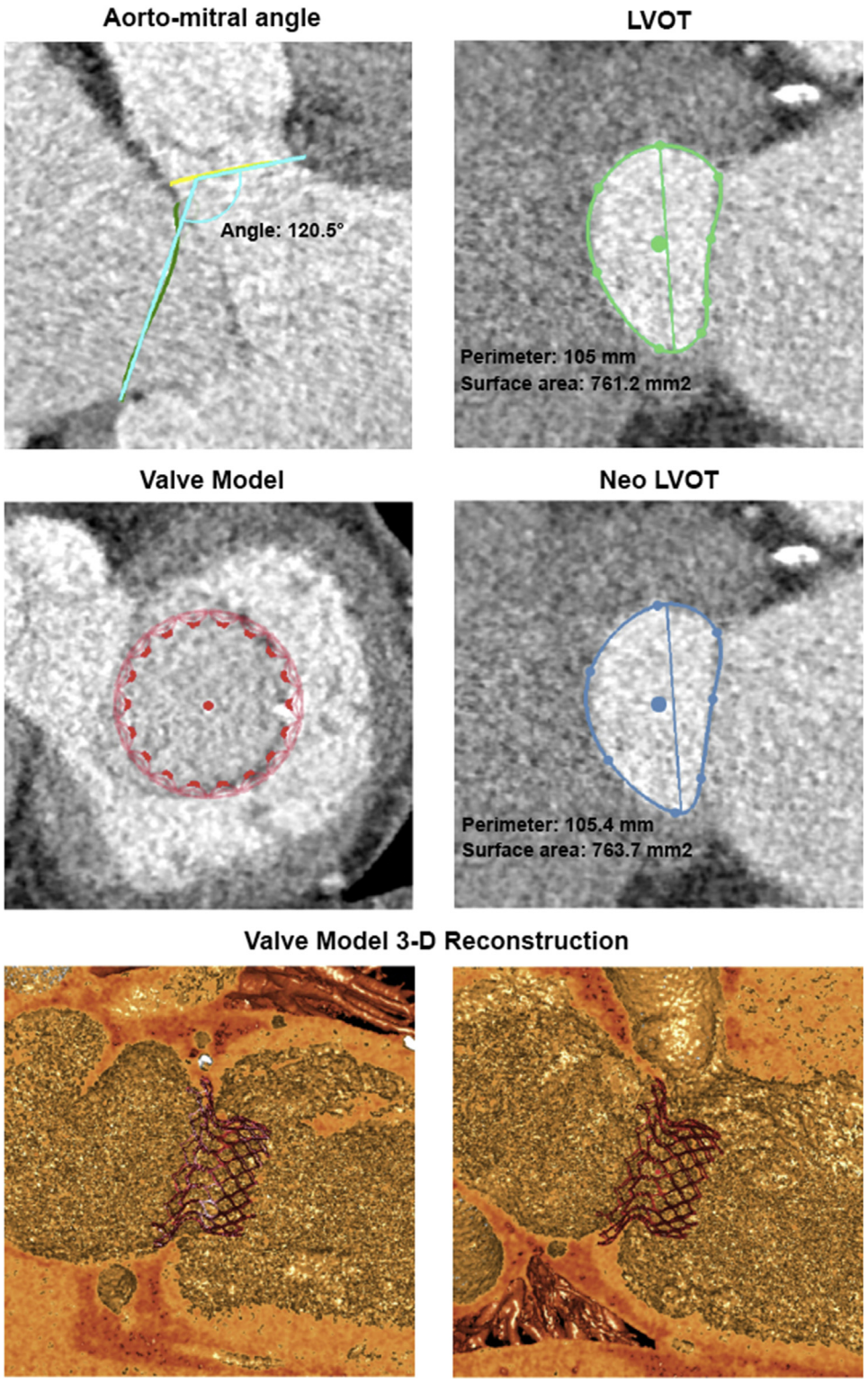
FIGURE 2 Mitral Annulus



The mitral annulus was tracked by manually placing several segmentation points for cubic spline interpolation along the insertion of the posterior mitral leaflet and along the contour of the anterior peak comprising the fibrous intervalvular continuity.

PATIENT #2. Patient #2 (Table 1) was a 65-year-old woman with severe idiopathic cardiomyopathy and severe functional MR. Comorbidities included chronic renal insufficiency and permanent atrial fibrillation. The patient had an implantable cardioverter-defibrillator-cardiac resynchronization therapy and she had multiple previous in-hospital admissions for heart failure despite optimal medical and cardiac resynchronization therapy. The echocardiography showed severe functional mitral and tricuspid regurgitation with an LV ejection fraction of 25% and severe right ventricle dysfunction (tricuspid annular plane systolic excursion, 11 mm). As for the first patient, she was deemed too high risk for surgical mitral valve replacement (Logistic EuroScore 2, 4.5%) and not a good candidate for the MitraClip or CardioBand secondary to poor mitral coaptation height and unfavorable anatomy of the interatrial septum.

FIGURE 3 **LVOT Patency Assessment by Multislice Computed Tomography**



Multislice computed tomography images of LVOT patency assessment. 3-D = 3-dimensional; LVOT = left ventricle outflow tract.

TABLE 1 Pre-Operative Clinical and Echocardiographic Characteristics of the Patients

	Age (yrs)	Sex	Logistic ES 2	EF (%)	MR Grade	MR Type	AR Grade
Patient #1	69	Male	8.9	25	Severe	FMR	None
Patient #2	65	Female	4.5	25	Severe	FMR	None

AR = aortic regurgitation; EF = ejection fraction; ES = EuroScore; MR = mitral regurgitation.

RESULTS

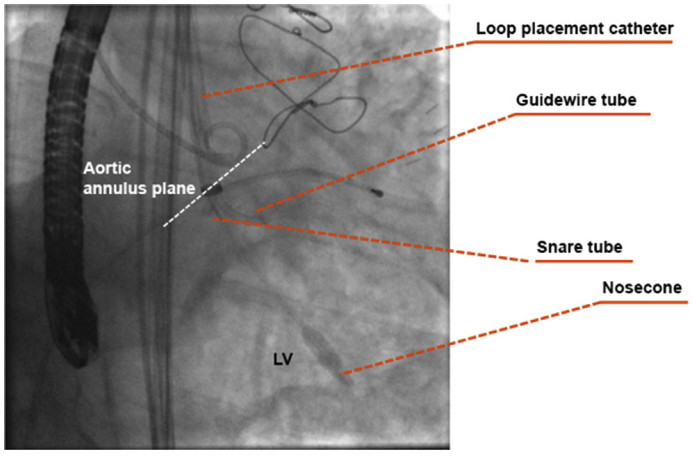
Both procedures were performed in the catheterization laboratory under fluoroscopic and transesophageal echocardiographic (TEE) guidance in general anesthesia and endotracheal intubation. Interventional cardiologists and cardiac surgeons formed the operating team.

After placement of a 10-F catheter Prostar XL (Abbott Vascular), an 18-F catheter GORE DrySeal sheath (W. L. Gore. & Associates, Flagstaff, Arizona) was introduced in the common right femoral artery. The LPC was advanced over a retrograde approach through the aortic valve inside the LV (**Figure 4**). One subannular tube was externalized (the second subannular tube was not used but later removed and replaced with a big snare), and using an "en face" view of the mitral valve, a 400-cm J-tipped Radifocus Guidewire Terumo (Shibuya, Tokyo, Japan) was advanced to reach around the mitral subannular space up to the ascending aorta (Online Video 1). The LPC was then retrieved back to the aortic arch and the guidewire was caught with a snare, extending out of the LPC. (Online Video 2). The temporary loop was then used to cinch the mitral subannular structures by pulling both the guidewire and the snare. If the TEE revealed that the loop was stacked in basal cords (eccentric cinching of the loop and/or dragging of cardiac walls), the loop was re-established until we ensured that the loop was free from impingements by the basal cords (Online Videos 3 and 4). That happened 6 and 8 times during the first and the second procedure, respectively.

Once the loop was obtained, the guidewire was pulled back and externalized from the femoral access. As a result, a guidewire loop was placed, entering the femoral access traveling up to the LV around the subannular apparatus and traveling back to the ipsilateral iliofemoral axes and externalized from the 18-F catheter sheath. At this stage the procedure is still fully reversible. Throughout this step of the procedure, both patients remained hemodynamically stable; many premature ventricular contractions and short episodes of ventricular tachycardia were reported. No episodes of ventricular fibrillation or sustained ventricular tachycardia were observed.

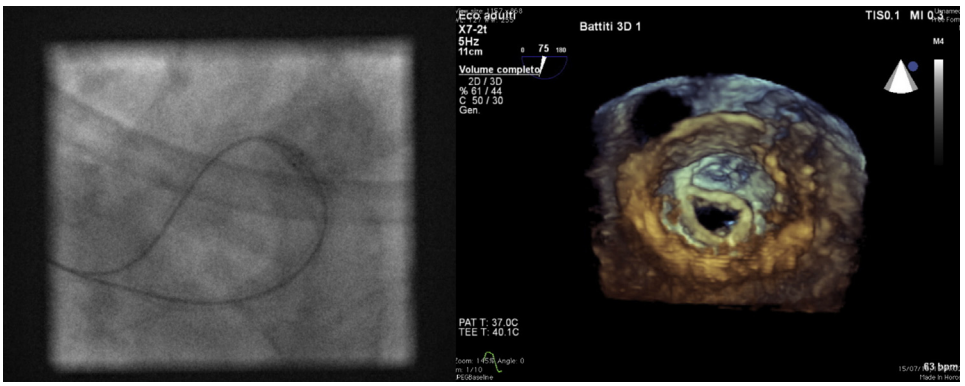
The delivery and closure of the SAI was done with a dedicated 18-F catheter SDC hosting the SAI and the 2 ends of the previously placed guidewire loop. The SDC was threaded over the 2 ends of the guidewire loop in the LV and the SAI was closed over the guidewire loop (**Figure 5**, Online Video 5). Once the SAI was secured, an anterior minithoracotomy was performed to access the LV apex with the placement of 2 octagonal pledgeted sutures. The apex was punctured in a standard fashion and a soft J-tipped wire was inserted and advanced through the mitral valve. A 7-F catheter introducer was then inserted and a pre-shaped 260-cm × 0.035-inch J-tipped guidewire (Amplatz Super Stiff, Boston Scientific, Natick, Massachusetts) was placed in the upper pulmonary vein. A 10/40-mm inflated balloon was tracked on the wire from the LV to the left atrium to ensure that the wire was not caught in the mitral apparatus. The 39-F catheter delivery system was directly inserted into the LV and across the mitral valve into the mid-left atrium. Coaxiality and alignment of the transcatheter mitral valve to the SAI were confirmed with 3-dimensional TEE and fluoroscopy. The delivery catheter was positioned in a way that allows the prosthetic valve's outflow to completely deploy in the ventricle, distal to the SAI, while the inflow port of the valve was still retained in the catheter. The valve outflow is brought into contact

FIGURE 4 Loop Placement Catheter



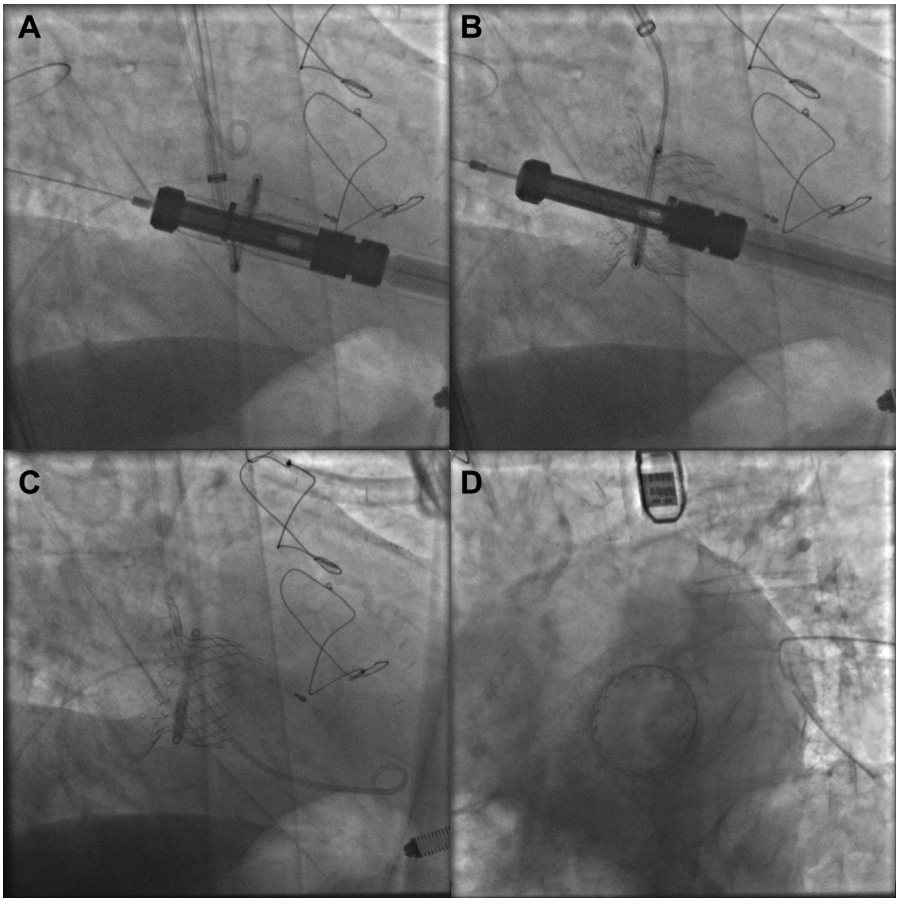
The loop placement catheter is advanced through the femoral artery and placed just across the aortic valve (Online Videos 1, 2, 3, and 4). LV = left ventricle.

FIGURE 5 Subannular Implant Deployment



Fluoroscopic "en face" view **(left)** and 3-dimensional transesophageal echocardiography short-axis view **(right)** of the subannular implant obtained during the procedure performed in Patient #1 (Online Video 5).

FIGURE 6 Transapical Mitral Valve Implantation Procedure



(A) Advancement of the transapical mitral valve implantation system across the mitral valve and the subannular implant into the left atrium. **(B)** Full deployment of the atrial portion of the bioprosthesis in the left atrium. The subannular implant is still attached to the loop placement catheter. **(C)** Fluoroscopic 3-chamber view of the transcatheter mitral valve. **(D)** Fluoroscopic "en face" view of the transcatheter mitral valve. See Online Video 6.

TABLE 2 Procedural Timing

	Loop Placement	SAI Release	Valve Deployment*	Duration
Patient #1	2:40	0:21	0:46	4:05
Patient #2	2:15	0:30	0:42	3:55

*From skin incision to skin closure.
SAI = subannular implant.

with the SAI by manually pushing the device toward the atrium, and the SAI is further pushed until it was pressed against the subannular groove. Then the inflow end of the transcatheter mitral valve is deployed from the delivery catheter (Figure 6). The catheter is closed and removed from the patient's heart and the access to the apex was closed. The guidewire loop was removed from the SAI and the SDC by pulling on 1 end.

Procedural times of both cases were around 4 hours (Table 2). Both patients remained hemodynamically stable during the whole procedures (Patient #2 was supported with a low dose of dobutamine from the beginning of the procedure). A post-implant LV angiogram showed mild intraprosthetic MR, and the absence of LVOT obstruction. TEE revealed secure seating of the prosthesis with normal valvular function and mild intraprosthetic MR (Online Video 6), no periprosthetic leak, transvalvular gradient of 4 to 6 mm Hg, and effective orifice area of 2.5 and 3.4 cm^2 (Online Video 7). Both patients had residual aortic regurgitation graded as mild-to-moderate that was not present before the procedure (Table 3). This finding was explained by the several maneuvers across the aortic valve performed during the loop placement attempts that may have slightly torn the aortic cusps. Potential damage to the aortic cusps can be avoided by reducing the maneuvers of the SDC, which are maintained stable across the aortic valve.

Patient #1 was transferred to the cardiac intensive care unit. On post-operative day 10, he experienced an episode of ventricular fibrillation treated with direct current shock. An implantable cardioverter-defibrillator was then implanted. Otherwise the post-procedural course was uneventful and the patient was transferred to a cardiac rehabilitation facility 2 weeks' post-implant in good hemodynamic status. At discharge, the transthoracic echocardiogram showed the mitral bioprosthesis well seated with mild central regurgitation and paraprosthetic leak. LV ejection fraction was unchanged as compared with the baseline (30%). At 5-month follow-up, the patient was in New York Heart Association functional class II. Mitral bioprosthesis performance compared favorably with that reported at discharge. Aortic regurgitation was mild.

Patient #2 experienced a successful procedure from technical standpoint. The valve was well functioning and residual mitral and aortic regurgitations were mild. However, the LV did not tolerate the reduction of MR and despite high doses of inotropic agents the left ventricular function rapidly deteriorated. The patient expired on Day 4 post-procedure.

TABLE 3 TEE Assessment at the End of the Procedure

	Intraprosthetic Leak	PVL	Prosthesis EOA (cm^2)	Mean Transmitral Gradient (mm Hg)	LVOT Obstruction	AR Grade
Patient #1	Mild	None	2.3	4	No	Moderate
Patient #2	Mild	None	3.5	3	No	Mild

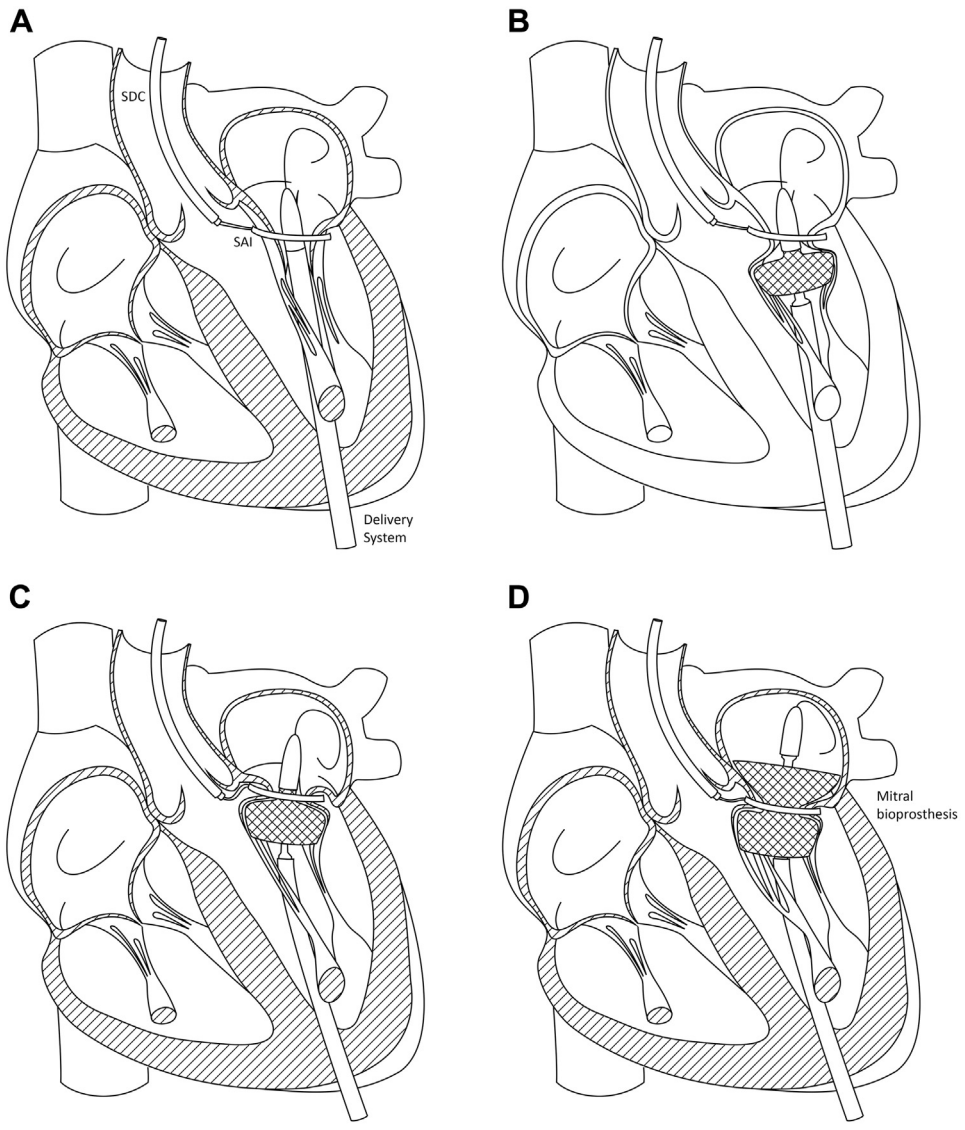
EOA = effective orifice area; LVOT = left ventricle outflow tract; PVL = paravalvular leak; TEE = transesophageal echocardiogram; other abbreviation as in Table 1.

STUDY LIMITATIONS. Our study is limited by the low number of patients and the short follow-up period. Ongoing compassionate implantation of the HighLife device and continuing follow-up of the treated patients will define the safety, reproducibility, and efficacy of this procedure.

CONCLUSIONS

The HighLife transcatheter mitral valve is a 2-component, catheter-based mitral implantation system specifically designed to treat severe MR. The cases here described showed that this approach is technically feasible. The peculiarity of this technology stands in the placement of the SAI that facilitates the implantation of the prosthesis and guarantees an extremely secure and effective sealing. The locking mechanism of the SAI was safe and secure as demonstrated in our case and in chronic animals (6). In addition, both the valve and the ring are covered with Dacron and are completely endothelialized after a few months. At that point, the implants are embedded in the anatomy and it can be expected for them to be even more stable than when they were implanted. There is 1 ring for 1 valve, and the ring always closes to the same size. Currently only 1 valve and 1 ring are available; however, the company is working on a second size for the future. The concept is also unique concerning the prevention of LVOT obstruction by pulling and fixing/fastening the anterior mitral leaflet instead of pushing it into the LVOT

FIGURE 7 Interaction Between the Subannular Implant and the Mitral Bioprosthesis



(A) The SAI is in place, the valve delivery system is advanced through the apical access. **(B,C)** The ventricular portion of the mitral prosthesis is released and the delivery system is pushed toward the left atrium. **(D)** The mitral bioprosthesis is completely deployed. Schematic representation of the interaction between the subannular implant and the mitral bioprosthesis (Online Video 7). SAI = subannular implant; SDC = subannular implant delivery catheter.

(Figure 7). Compared with other systems, the usually large size of mitral annulus might not be a major concern. The placement of the loop represents an important challenge of this step of the procedure and still requires substantial refinements in terms of materials and technique. However, it should be underlined that this step of the procedure had no impact on the hemodynamic status and it is completely reversible. Finally the presence of the SAI, which acts as a big fluoroscopic marker, facilitates remarkably the delivery of the prosthesis.

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PERSPECTIVES

WHAT IS KNOWN? TMVI represents a promising approach to treating mitral regurgitation in patients at increased risk of perioperative mortality.

WHAT IS NEW? This first-in-human description demonstrated that TMVI using the 2-component HighLife system is technically feasible and can be performed safely.

WHAT IS NEXT? Additional cases and well-conducted studies are needed to assess the efficacy of the HighLife technology for the treatment of severe mitral regurgitation.

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KEY WORDS mitral regurgitation, prosthesis, transcatheter mitral valve replacement

APPENDIX For supplemental videos and their legends, please see the online version of this article.