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PII: S0735-1097(15)06686-3

DOI: 10.1016/j.jacc.2015.09.068

Reference: JAC 21873

To appear in: *Journal of the American College of Cardiology*

Received Date: 25 August 2015

Revised Date: 18 September 2015

Accepted Date: 24 September 2015

Please cite this article as: Campelo-Parada F, Perlman G, Philippon F, Ye J, Thompson C, Bédard E, Abdul-Jawad Altisent O, del Trigo M, Leipsic J, Blanke P, Dvir D, Puri R, Webb JG, Rodés-Cabau J, First-in-man Experience of a Novel Transcatheter Repair System for Treating Severe Tricuspid Regurgitation, *Journal of the American College of Cardiology* (2015), doi: 10.1016/j.jacc.2015.09.068.

First-in-man Experience of a Novel Transcatheter Repair System for Treating Severe Tricuspid Regurgitation

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Short title: Transcatheter Treatment of TR

Relationship with industry: Drs. Webb and Rodés-Cabau are consultants for and have received research grants from Edwards Lifesciences. The other authors have not reported any potential conflict of interest with respect to this manuscript.

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ABSTRACT

Background. Isolated tricuspid valve surgery is associated with high morbidity and mortality, especially in patients with prior cardiac surgery. The transcatheter Forma Repair System (Edwards Lifesciences, Irvine, California) is designed to provide a surface for native leaflet coaptation to reduce tricuspid regurgitation (TR) by occupying the regurgitant orifice area.

Objective. To evaluate the feasibility and exploratory efficacy with this transcatheter repair system for the treatment of severe TR.

Methods. Seven high-risk patients with severe TR and clinical signs of heart failure were declined for surgery and offered transcatheter treatment with the device. All procedures were performed within a cardiac catheterization laboratory or hybrid operating room under general anesthesia with transesophageal echocardiographic guidance. Vascular access was via the left axillary vein. Baseline characteristics, procedural and in-hospital outcomes, as well as 30-day follow-up were prospectively collected.

Results. All patients had severe TR and NYHA class II-IV (mean age of 76±13 years; mean Logistic EuroSCORE of 25.7 ± 17.4%), and underwent device implantation to improve tricuspid leaflet coaptation thereby reducing TR. Device implantation was successful without procedural complications in all patients, with significant reductions in TR severity (moderate in 3 patients and mild in 4). Median hospital length-of-stay was 4 days. At 30-day follow-up, all patients but 1 demonstrated improvements in NYHA functional status (to class II) with pronounced reductions in the presence and severity of peripheral edema. TR severity was assessed as being moderate at 30-day TTE follow-up in all patients. No complications related to the device or vascular access were observed during follow-up.

Conclusions. A transcatheter-based treatment option for severe TR appears safe and feasible with the repair system. Improvements in TR severity were documented in all patients, which were accompanied by improvements in peripheral edema and NYHA functional class.

Key words: transcatheter valve tricuspid repair; valve surgery; valve repair

Abbreviations

AF: atrial fibrillation
CT: computed tomography
LVS: left-sided valve surgery
RV: right ventricle
TEE: transesophageal echocardiography
TR: tricuspid regurgitation
TTE: transthoracic echocardiography

Despite its association with poor survival, severe tricuspid regurgitation (TR) is an under-recognized and under-treated condition; its clinical consequences being independent of age, left ventricular ejection fraction, or pulmonary artery pressures (1). Moderate-to-severe TR is present in 1.6 million U.S individuals, yet <0.5% of this population underwent surgical tricuspid repair or replacement (2). In patients undergoing left-sided valve surgery (LVS), concomitant tricuspid valve repair is universally recommended in the presence of severe coexistent TR (3,4). Moreover, the role of surgical intervention for symptomatic severe TR late following LVS remains unclear. Isolated tricuspid valve surgery is associated with significant in-hospital mortality and poor long-term survival, especially in patients with prior mitral or aortic valve surgery (5,6).

In this regard, alternative minimally invasive surgical and percutaneous transcatheter treatment alternatives were recently developed in an attempt to improve the prognosis and quality of life of patients with severe TR. Novel treatment options include percutaneous annular rings, transcatheter suture bicuspidization, valved stents or heterotopic placement of transcatheter aortic valves in the vena cava (7-9). The Forma Repair System (Edwards Lifesciences, Irvine, California) is a novel transcatheter treatment alternative for patients with severe TR and prohibitive operative risk. The device is designed to reduce severe TR by occupying the regurgitant orifice area and providing a surface for native leaflet coaptation. Herein we describe the first-in-man device experience with this novel therapeutic concept, focusing on the safety, feasibility, and preliminary efficacy in reducing severe TR and right heart failure at 30-day follow-up.

METHODS

Patient screening

Patients with severe TR and symptoms of heart failure, deemed to be at high surgical risk, were considered suitable candidates for this novel device. Only patients with functional TR and without pacemaker/ICD leads or prior tricuspid surgery were considered. Following careful evaluation by a Heart Team, surgical tricuspid valve repair or replacement was deemed to be associated with an unacceptable surgical risk. All procedures were approved by Health Canada under a Special Access program, and all patients provided signed informed consent for the procedures.

TR severity was assessed by transthoracic echocardiography (TTE) in all patients. In some patients, transesophageal echocardiography (TEE) assisted in establishing the mechanism of regurgitation and the presence of multiple jets. TR severity was graded as follows: I (trace), II (mild), III (moderate) and IV (severe). The severity of TR was determined on the basis of the colour flow TR jet (large central and holosystolic jet with systolic flow reversal on hepatic veins) and the vena contracta width (≥7 mm) (10). Cardiac computed tomography (CT) was also used to measure tricuspid annular dimensions, right ventricular diameters and the distance from the valvular annulus to the right ventricular apex. Finally, subclavian and axillary left veins were assessed by CT to ensure their size was compatible with the introducer sheath and the device.

Device concept

This transcatheter repair system is designed to reduce TR by occupying the regurgitant orifice area and providing a surface for native leaflets coaptation (**Figure 1; Central Illustration**). The device consists of a spacer and a rail which is anchored at the right ventricular apex. The spacer is a foam filled polymer balloon that passively expands via holes in the spacer shaft. Two radiopaque markers help to initially position the spacer using fluoroscopy. There are 2 spacer sizes currently available (12 mm and 15 mm), with a length of 42 mm. The device is

fixed at the distal end in the right ventricular myocardium. The fixation mechanism consists of a 6-pronged nitinol anchor that is designed to minimize both the risk of penetration of the epicardial surface and the prong exposure in the right ventricle. It includes a retainer ring for avoiding a deep deployment of the anchor into the myocardial wall.

Procedure

Procedures were undertaken within a cardiac catheterization laboratory or hybrid operating room using general anesthesia. During all stages of device implantation, fluoroscopic guidance coupled with 2D or 3D-TEE was utilized to ensure optimal device positioning. Following left axillary vein access, a 24F sheath was secured in place to accommodate the largest spacer size (15 mm). Right ventriculography was performed to locate the tricuspid annular plane and right ventricular apex (**Figure 2A**). An ideal target location is identified to allow the device to be perpendicular to the valve plane (**Figure 2A)** as well as to allow all leaflets to coapt with the device. The anchor site is aimed at the right ventricular wall perpendicular to the center of the annulus. A steerable delivery catheter is positioned within the right ventricle to deliver the rail system to the ideal location **(Figure 2B)**. The spacer is then tracked over the rail to the tricuspid valve plane and placed in the best position to reduce TR, assessed live with TEE. (**Figure 2C/2D**) The device is then locked proximally and the excess rail length is coiled and placed within a subcutaneous pocket (**Figure 3**). The entire device is fully retrievable during all stages of the procedure if needed until sheath removal.

Post-procedure and follow-up

Post-procedure, patients were admitted to a cardiology ward for clinical observation. A post-procedure TTE verified appropriate device positioning and the degree of residual TR. Rail system integrity and position were also confirmed with cardiac-CT and/or chest X-ray. First

post-procedural follow-up was scheduled at 30 days along with TTE, chest X-ray, blood tests and clinical examination. Baseline characteristics of all patients, procedural and hospital outcomes as well as results of follow-up were prospectively collected. This is a descriptive study and no statistical analyses were performed.

RESULTS

Baseline characteristics

A total of 11 patients were considered potential candidates to device implantation. Of these, 4 patients were excluded due to the following reasons: decision of surgical tricuspid replacement (1 patient), concomitant gastric cancer with limited expected survival (1 patient), extremely dilated right ventricle and tricuspid annulus with very large coaptation defect (1 patient), and previous chest radiotherapy leading to a lack of sufficient subcutaneous and muscular tissue to accommodate the pocket where the excess rail length of the device system is placed (1 patient). A total of 7 patients were finally enrolled in this initial experience with the device and their baseline clinical characteristics are described in **Table 1**. Mean age was 76 ± 13 years and the mean Logistic EuroSCORE was 25.7 ± 17.4%. All patients at baseline presented with a normal left ejection fraction (56 ± 5 %) and New York Heart Association (NYHA) functional class III or IV (6 patients, one patient was in class II). Pulmonary hypertension was observed in 5 patients and 5 patients had prior cardiac surgery (prior coronary artery bypass grafting in all with aortic or mitral valve surgery in 4 of them). Permanent atrial fibrillation (AF) was present in 5 patients and 6 patients had renal insufficiency, one of whom was dialysis-dependent. The mean baseline daily furosemide dose was 80 ± 61 mg. All patients had baseline concomitant mild or mild-to-moderate mitral regurgitation. Tricuspid valve vena contracta was measured in the 2 and 4 chambers views on TTE. Mean maximal vena contracta in this group of

patients measured 15.5 ± 5.1 mm; a consequence of leaflet non-coaptation with resultant severe, symptomatic TR.

Procedural, in-hospital and 30-day results

Table 2 summarizes procedural results and in-hospital outcomes. All patients underwent successful device implantation without procedural complications. One 12-mm device was retrieved and replaced for the largest 15 mm device during the same procedure to achieve a better result. The degree of TR was reduced intra-procedurally by at least 1 degree in all patients, and 4 patients had a reduction of 2 degrees (up to mild TR). New-onset AF appeared in 1 of the 2 patients without AF at baseline. One patient experienced several episodes of asymptomatic non-sustained ventricular tachycardia during the 24hrs following the procedure, originating from the RV and subsequently controlled with beta-blockers. In 2 other patients, frequent premature ventricular contractions (couplets or triplets) were seen during the first day post-intervention. One patient experienced minor bleeding related to vascular access. The same patient had a more prolonged hospitalization due to pneumonia and renal failure. The median hospital length-of-stay was 4 (3-6) days. All patients but 1 received vitamin K blockers as antithrombotic therapy following the procedure.

Tables 3 and 4 describe outcomes at 30-days post-procedure. All patients were alive and completed the 30-day follow-up. No additional complications occurred between hospital discharge and 30-day follow-up. All patients but 1 demonstrated improvement in their NYHA functional status to class II (the patient in class II at baseline had no change in the functional class at follow-up) coupled with significant reduction in peripheral edema. Diuretic dosage was reduced in 2 patients at first clinical follow-up. No other significant changes in patient's medication were noted. TR was assessed as being moderate in severity at the 30-day TTE in all

patients and there was no apparent iatrogenic tricuspid stenosis resulting from the device (**Figure 4, Central Illustration**). A total of 4 and 5 patients had quality of life (Kansas City Cardiomyopathy Questionnaire) and exercise capacity (6-minute walk test) evaluation at baseline and at 30-day follow-up, respectively. Quality of life improved in all of these 4 patients (from 59.6±14.1 to 86.2±5.4), and exercise capacity improved in 4 out of 5 patients (mean 6MWT distance of 297±66 to 326±74 meters) (**Central Illustration**). One patient failed to complete the total 6-minute duration due to arthritic joint pain (although at 5 minutes the distance covered was greater than pre-device insertion). No ongoing device or vascular access-related complications or infection were documented at 30-day follow-up.

DISCUSSION

This repair system is a novel transcatheter treatment option for significant TR. In this seminal series of 7 patients who were a high or prohibitive risk for surgery, all of them underwent successful device implantation without major procedural complications. All patients demonstrated improvements in TR severity, peripheral edema and NYHA functional class. Furthermore, no significant access site or device-related complications were seen at 30-days post-procedure.

TR is not a benign condition, with a step-wise relationship between TR severity and mortality rates (11). In patients undergoing mitral valve surgery, concomitant and untreated moderate or severe TR is associated with lower mid-term survival rates(12). In a large series published by Nath et al (1), 1-year survival was 63.9% in those with severe TR, independent of age, biventricular systolic function, RV size and the degree of inferior vena cava dilatation. Despite this knowledge, isolated tricuspid valve repair or replacement seldom occurs, invariably occurring concomitantly at the time of LVS(13). Current European and AHA/ACC Guidelines

on valvular heart disease recommend concurrent TV repair at the time of LVS if the TV annulus is dilated, even if TR is found not to be severe (3,4). This more aggressive criterion is aimed to avoid ongoing significant TR progression during follow-up (14,15). Isolated tricuspid valve surgery late following initial LVS is associated with poor clinical outcomes and with in-hospital mortality rates approaching 10% (5,13). However, other studies reported better outcomes using less invasive access via a right lateral thoracotomy(16) . As such, there is an ongoing unmet clinical need for less-invasive yet effective treatment options for patients with significant TR left surgically untreated.

During recent years, and following the success of other percutaneous devices for treating structural heart disease, there is a growing interest in novel treatment paradigms for this often neglected valve lesion. Percutaneous treatment options represent an important alternative in patients deemed at high surgical risk who are refractory to medical therapy alone. However, there is currently a paucity of data relating to the feasibility, safety and results of various percutaneous tricuspid devices. A percutaneous bicuspidization of the tricuspid valve was achieved using the Mitralign system (Mitralign Inc., Tewksbury, Massachusetts). This transcatheter device, based upon pledgeted sutures and designed to plicate the mitral annulus, was successfully implanted in a patient with severe TR (7). The TriCinch System (4Tech, Dublin, Ireland) is currently being evaluated in a Phase 1 trial. It achieves a tricuspid annular reduction via a transfemoral approach by applying tension with a Dacron band anchored at the tricuspid annulus and inferior vena cava (17). Transcatheter tricuspid valve implantation in native valves has thus far only been reported in animal models using custom-made valves (18-20). In patients with degenerated tricuspid bioprostheses or failed surgical annuloplasty rings, the presence of this rigid structure allows safe valve implantation with a transcatheter aortic or

pulmonic valve (21,22). The implantation of valves at the inferior cavoatrial junction or both superior and inferior vena cava was also reported with satisfactory hemodynamic outcomes, initially with a custom-made self-expandable valve and later with a Sapien XT valve (Edwards Lifesciences, Irvine, California), with associated positive RV remodeling noted in the first group of patients (8,9,23). A transatrial intrapericardial tricuspid annuloplasty device, consisting of a circumferential device deployed within the pericardial space to modify tricuspid annular dimensions and reduce functional TR, was reported in an animal model (24). Another device under preclinical development (Millipede, LLC, Ann Arbor, Michigan), is a tricuspid annuloplasty ring, which can be attached percutaneously or via minimally invasive surgery (25).

A key differential design feature of this transcatheter repair system is the presence of a spacer. The initial experience with this device demonstrated no major safety issues coupled with a high rate of successful implantation. When evaluating the efficacy of the device in reducing TR severity, the presence of the spacer between the valve leaflets makes it difficult to accurately assess TR severity post-device implantation, as vena contracta size and effective regurgitant orifice areas are difficult to quantify. Consequently, only a qualitative analysis of color Doppler flow was possible to evaluate post-procedural results. At 30-days post-procedure, all patients demonstrated TR quantified as moderate in severity. One possible explanation for the small degree (1 degree) of TR reduction measured qualitatively with TTE possibly relates to the large mean baseline vena contracta size in our cohort. The mean vena contracta size was of similar magnitude to the largest-sized spacer currently available (15 mm). Despite good device positioning, complete coaptation was however not achieved, resulting in significant residual degree of post-procedural TR. Also, the very advanced stage of the disease in most patients may have played a role in the mild reduction in TR at 30 days. Nevertheless, we observed that a

reduction from severe to moderate TR seemed sufficient to impart significant reductions in signs of right heart failure as well as improving functional status in all patients. As such, larger studies will need to be undertaken to further test the safety and efficacy of this novel device. Specific criteria for quantifying right ventricular dysfunction and pulmonary hypertension, along with novel quantitative echocardiographic imaging criteria may be required for optimizing patient selection for transcatheter tricuspid devices such as the Forma device. It is conceivable that larger than currently available spacer sizes may be required to improve echocardiographic results in patients with large non-coaptation defects and vena contracta. Some increase in the severity of TR was observed in 4 patients 30 days after the procedure. Whereas this may be related to the use of procedural TEE under general anesthesia versus TTE without anesthesia at 30 days, follow-up imaging studies are mandatory to determine the long term beneficial effects of the device.

Limitations

The evaluation of baseline and 30-day exercise (6MWT) capacity and quality of life exams were not systematically performed in all patients. Echocardiography data was not evaluated in a centralized echo core lab. No magnetic resonance imaging exams were performed to evaluate RV function and TR severity following the procedure due to the lack of data on device magnetic resonance compatibility. Finally, there was no systematic evaluation of BNP levels.

In conclusion, transcatheter reduction of secondary tricuspid valve regurgitation appears safe and feasible with this transcatheter repair system. TR reduction was observed in all patients, along with improvements in peripheral edema and functional class. Longer-term follow-up and larger studies are required to confirm these preliminary results.

PERSPECTIVES

Competency in Patient Care and Procedural Skills: In patients with severe, symptomatic secondary tricuspid regurgitation (TR) at high surgical risk, transcatheter reduction therapy can be performed with a low short-term risk of complications and may represent an acceptable alternative strategy.

Translational Outlook: Further studies are necessary to establish the long-term efficacy of transcatheter interventions to improve right heart failure, functional status and quality of life in patients with severe secondary TR.

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FIGURE LEGENDS

CENTRAL ILLUSTRATION: **Novel Transcatheter Repair System for Severe Tricuspid Regurgitation: Exercise capacity and quality of life before and after device implantation.** (Top Panel) Six-minute walk test (6MWT) and Kansas City Cardiomyopathy Questionnaire of Quality of life (KCCQ) results before device implantation and at 30-day follow-up in 5 and 4 patients, respectively. (Bottom Panel) The Forma device showing the anchor system at right ventricular apex, spacer at tricuspid valve annulus and locking system at left subclavian vein.

Figure 1. **The Forma Repair System**. A) Spacer B) Steerable delivery catheter and anchoring system. C) Device at the tricuspid valve annulus, anchoring system at the right ventricular apex and excess device length coiled into a subcutaneous pocket.

Figure 2. **Intra-procedural fluoroscopic/angiographic images**. A) Right ventriculography to locate the tricuspid annular plane and identify the ideal anchor location on fluoroscopy. B) Right ventricular anchoring via a steerable delivery catheter. C) Device positioning in the valve plane. D) Final right ventriculography with the device in correct position (red arrow) and reduction of tricuspid regurgitation from baseline.

Figure 3. **X-ray images of the device after implantation.** A) Chest X-ray after device implantation. B) Image detail showing the 2 radiopaque markers of the coaptation system and the anchor at the right ventricle.

Figure 4. **Echocardiography images before and after device implantation.** Apical 4-chamber-view of transthoracic echocardiography of the same patient before (left) and after the device implantation (right).

Table 1: Baseline clinical and echocardiographic characteristics

Variable	N=7
Age, years	76±13
Sex, male	4 (57)
NYHA class ≥ III	6 (86)
Coronary artery disease	6 (86)
Prior open heart surgery	5 (71)
Prior valve surgery	4 (57)
Mitral	2 (29)
Aortic	2 (29)
COPD	1 (14)
Permanent atrial fibrillation	5 (71)
Pulmonary hypertension	5 (71)
Creatinine clearance <60 mL/min (eGFR)	6 (86)
Hemodialysis	1 (14)
Logistic EuroSCORE (%)	25.7±17.4
6 minute walk test (meters)	297±66
Kansas City Cardiomyopathy Questionnaire	59.6±14.1
Daily furosemide dose (mg)	80±61
Baseline Echocardiogram	
LVEF (%)	56±5
PAPs (mmHg)	69.7±6.0
MR grade	
Mild	3 (43)
Mild to moderate	3 (43)
Moderate	1 (14)
Severe TR grade	7 (100)
Vena contracta (mm)	15.5±5.1
TAPSE (mm)	16.5±4.2
TAPSV (cm/s)	10.6±2.0
RV diameter (mm)	47±7
Baseline CT data	
Tricuspid valve major diameter (mm)	50.3±6.0
Tricuspid valve minor diameter (mm)	43.2±2.0

Values are expressed as n (%) or mean (±SD) except for hospitalization length

NYHA: New York Heart Association. COPD: Chronic Obstructive Pulmonary Disease. eGFR: Estimated Glomerular Filtration Rate. LVEF: Left Ventricular Ejection Fraction. PAPs: Systolic Pulmonary Artery Pressure. MR: Mitral Regurgitation. TR: Tricuspid Regurgitation. RV: Right Ventricle. TAPSE=Tricuspid Annular Plane Systolic Excursion, TAPSV=Tricuspid Annular Peak Velocity CT: Computed Tomography.

Table 2: Post-Procedural and In-Hospital Outcomes

Variable	N=7
Procedural results	
Successful device implantation	7 (100)
Conversion to open heart surgery	0 (0)
Device retrieval	1 (14)
Cardiac tamponade	0 (0)
Access site complication	1 (14)
Procedural time (skin to skin, min)	122±34
Contrast volume (mL)	71±32
Venous closure	
Surgical suture	5 (71)
Percutaneous*	2 (29)
Intraprocedural TEE TR reduction >1 grade	7 (100)
Hospital outcomes	
Renal failure	1 (14)
Conduction disturbance/arrhythmia	2 (29)
Bleeding (VARC-2 criteria)	
Minor	1 (14)
Major	0 (0)
Vascular or access site complication	
Minor	1 (14)
Major	0 (0)
Pneumonia	1 (14)
Pulmonary embolism	0 (0)
Hospitalization length (days), median (IQR)	4 (3-6)
In hospital mortality	0 (0)

Values are expressed as n (%) or mean (±SD) except for hospitalization length
*with the Proglide device (Abbot Vascular, Santa Clara, CA)
TEE: Transesophageal echocardiography. TR: Tricuspid Regurgitation. VARC-2: Valve Academic Research Consortium-2.

Table 3. Thirty-Day Follow-Up Outcomes

Variable	**N=7**
Death	0 (0)
NYHA class	
I	0 (0)
II	7 (100)
>III	0 (0)
Peripheral edema reduction	7 (100)
Furosemide dose reduction from baseline	2 (29)
Access site complication	0 (0)
6 minute walk test (meters)	326±74
Kansas City Cardiomyopathy Questionnaire	86.2±5.4
Re-hospitalization	0 (0)
Echocardiography data	
LVEF (%)	57±4
TR grade	
Mild	0 (0)
Moderate	7 (100)
Severe	0 (0)
Trans-tricuspid gradient (mmHg)	1.2±0.3
TAPSE (mm)	18.5±5.3
TAPSV(cm/s)	10.2±2.4
RV diameter	46±8

Values are expressed as n (%) or mean (±SD)

Abbreviations as in previous Tables

Table 4. Individual Changes in Tricuspid Regurgitation Severity, Right Ventricular Function, Exercise Capacity and Quality of Life

	TR degree (baseline, TTE)	TAPSE (mm, baseline)	RV-Diameter (mm, baseline)	KCCQ (baseline)	6MWT (baseline	TR degree (procedural , TEE)	TR degree (30-days, TTE)	TAPSE (mm, 30-days)	RV-Diameter (mm, 30-days)	KCCQ (30-days)	6MWT (meters, 30-days)
Patient #1	IV	14	57	62.02	261	II	III	10	55	82.85	293
Patient #2	IV	NA	41	NA	NA	II	III	NA	50	NA	NA
Patient #3	IV	NA	43	NA	NA	II	III	15	36	NA	NA
Patient #4	IV	21	40.5	45.95	250	III	III	18	39.8	87.1	240*
Patient #5	IV	12	40	52.21	237	III	III	24	40	81.38	298
Patient #6	IV	19	50	78.38	385	III	III	21	44.7	93.48	430
Patient #7	IV	NA	51	NA	350	II	III	23	48	NA	370

*Test stopped at 5 minutes due to arthritic joint pain

TR: tricuspid regurgitation; RV: right ventricle; TEE: transesophageal echocardiography; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWT: 6-minute walk test; TAPSE=Tricuspid Annular Plane Systolic Excursion , TAPSV=Tricuspid Annular Peak Velocity