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Improved right ventricular function following transapical transcatheter mitral valve implantation for severe mitral regurgitation

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ABSTRACT

Background: Transapical transcatheter mitral valve implantation (TMVI) may be a therapeutic option for patients with severe mitral regurgitation (MR) excluded from cardiac surgery due to excessive risk. Exclusion criteria frequently include pulmonary hypertension and right ventricular (RV) dysfunction. The effect of TMVI on RV function has not previously been well-characterized. The aim of this study was to examine the procedural and 3-month impact of TMVI on RV hemodynamics and function.

Methods: This was a multi-center, retrospective, observational cohort study of patients with >3+MR undergoing TMVI. Pre- and post-TMVI hemodynamics were assessed with right heart catheterization. RV function was assessed at baseline, pre-discharge and at 3-months by echocardiography.

Results: Forty-six patients (age 72±9 years; 34 men) with ≥3+MR underwent TMVI over a 5-year period. Successful device implantation was achieved in all patients with abolition of MR ($p < 0.001$) and reduction in left-ventricular end-diastolic volume ($p = 0.001$). RV stroke work index (RVSWI) increased intra-operatively (7 ± 4 g/m/beat/m^2 vs 11 ± 5 g/m/beat/m^2; $p < 0.001$). At 3-months there were reductions in severity of tricuspid regurgitation (TR) ($p < 0.001$) and pulmonary artery systolic pressure (PASP) (49 ± 16 mmHg vs 36 ± 12 mmHg; $p < 0.001$), and improvements in RV fractional area change (28 ± 7% vs 34 ± 9%, $p<0.001$), tricuspid annular plane systolic excursion (TAPSE) (1.0 ± 0.3 vs 1.5 ± 0.5cm, $p = 0.03$), and RV free wall longitudinal strain (−14.2±5.0 vs −17.6±7.3, $p = 0.05$).

Conclusions: Transapical TMVI results in significant improvement of RV function that is sustained to 3-months as evidenced by improvements in RVSWI and RV fractional area change, as well as reductions in PASP and TR severity.

1. Introduction

Right ventricular (RV) dysfunction in the setting of chronic mitral regurgitation (MR) is common and occurs as a result of intrinsic myocardial dysfunction, maladaptive left ventricular (LV) and left atrial (LA) remodeling, impaired ventricular septal motion, and pericardial constraint imposed by progressive LV volume overload [1–8]. Pulmonary hypertension secondary to severe MR exacerbates RV dysfunction by increasing RV afterload. RV dysfunction may be further exacerbated by tricuspid valve regurgita-

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tion (TR), which results from progressive RV and tricuspid annular dilatation. RV dysfunction has important prognostic implications following mitral valve surgery [9,10], and both impaired RV function and pulmonary hypertension are independent predictors of long-term post-operative cardiovascular mortality [2,3,11–13]. Patients with impaired RV function and significant pulmonary hypertension are frequently excluded from conventional surgical repair but might benefit from transcatheter mitral valve (MV) interventions.

Transapical transcatheter mitral valve implantation (TMVI) is an emerging therapeutic alternative to conventional MV surgery for patients deemed to be at prohibitively high risk (Fig. 1). TMVI has previously been reported to be safe, efficacious in the abolition of MR, and resulted in a reduction of LV end-diastolic and end-systolic volumes at 30-days and 1-year [14,15]. Although LV unloading is thought to reduce pericardial constraints on the right ventricle and improve overall RV function, to date, the acute off-pump changes to RV hemodynamics and function have not been described. The objective of this study was to examine the immediate and short-term impact of transapical TMVI using the Tendyne mitral valve system [14,15] on RV hemodynamics and function.

2. Methods

2.1. Study population

This was a multi-center, retrospective, observational cohort study of one-quarter of worldwide patients who underwent TMVI between October 2014 and October 2019 using the Tendyne system (Abbott Vascular, Santa Rosa, CA) [14,15]. The cohort included 41 patients enrolled in the Tendyne Expanded Feasibility Study and 5 patients treated under a Compassionate Use protocol. Inclusion criteria for the study were: age $\geq$ 18 years, MR grade 3 or 4 (primary or secondary), and symptoms of dyspnoea (New York Heart Association [NYHA] functional class $\geq$ II). Exclusion criteria included: LV end-diastolic diameter > 70 mm, severe mitral annular or leaflet calcification, left atrial or LV thrombus, prior mitral or aortic valve surgery, prior transcatheter mitral intervention, and/or a pulmonary artery systolic pressure $\geq$ 70 mmHg [14,15]. Details of the procedure and patient outcomes at 30-days and 1-year have been described previously [14,15]. Informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in prior approval by each institution's human research ethics committee. All demographic data were manually extracted from the electronic medical records.

2.2. Echocardiography

Each patient underwent 2D-transthoracic echocardiogram (TTE) before TMVI, 2D-TTE pre-discharge and further TTEs at 1 and 3-months. Patients were excluded if TTE data were not available or acquired outside the study time period. TTE images were obtained using an EPIQ 7 (Phillips Healthcare, Eindhoven, the Netherlands) or Vivid 95 (GE Medical Systems, Horten, Norway) ultrasound machine. Standardized measurements were performed at the time of image acquisition or offline using local hospital reporting systems in accordance with guidelines from the American Society of Echocardiography [16]. Measurements using 2D-speckle tracing echocardiography (STE) were performed offline using EchoInsight Pro (Epsilon Imaging, Michigan, USA) with a frame rate of at least 30 frames/s.

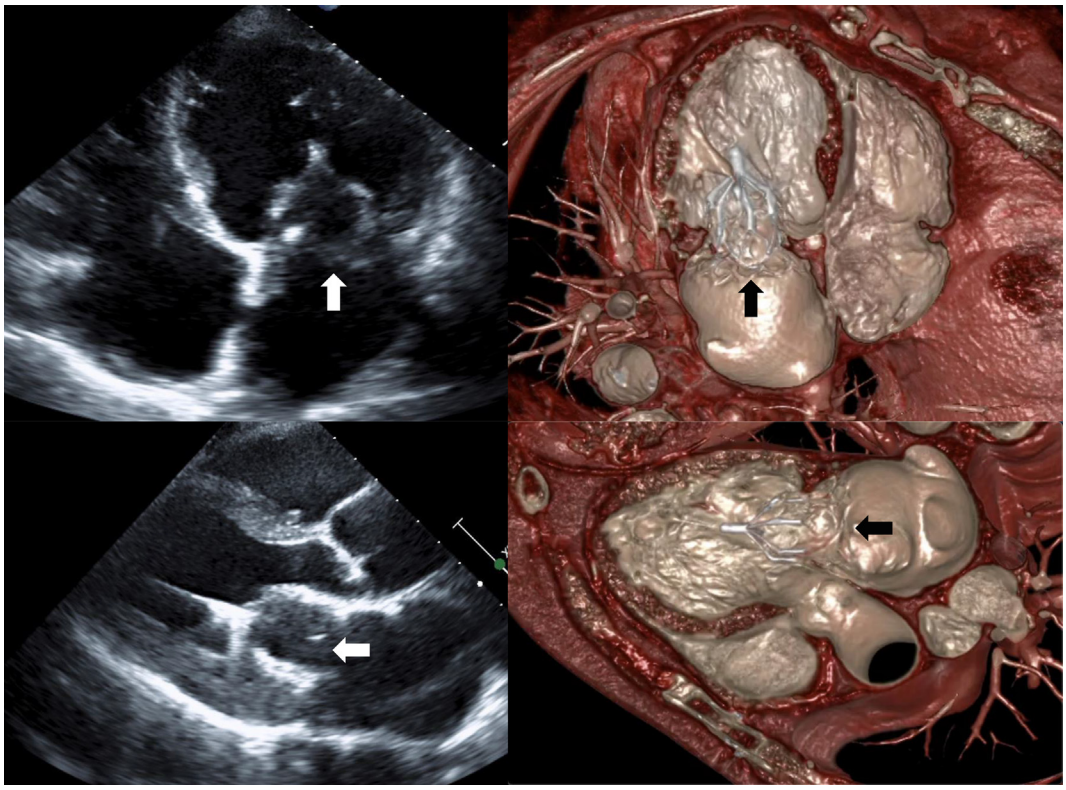

Fig. 1. TTE and cardiac CT images of Tendyne TMVI. Top: (Left) TTE four-chamber view demonstrating Tendyne TMVI and apical tether; (Right) cardiac CT four-chamber view demonstrating Tendyne TMVI and apical tether. Bottom: (Left) TTE parasternal long axis view demonstrating Tendyne TMVI and apical tether; (Right) cardiac CT apical two-chamber view demonstrating Tendyne TMVI and apical tether. CT images courtesy of Dr James Otton. Abbreviations: CT = computed tomography; TTE = transthoracic echocardiogram; TMVI = transcatheter mitral valve implantation.

Based on our hypothesis, patients were stratified into two groups according to the pre-operative LV ejection fraction (EF). LV function was quantified by recording LVEF using the Simpson's biplane method, LV end-diastolic dimension (LVEDD), end-systolic dimension (LVESD), end-diastolic volume (LVEDV), end-systolic volume (LVESV), LV global longitudinal strain (GLS), circumferential and radial strain.

Global RV systolic dysfunction was recorded qualitatively as a categorical variable (mild, moderate or severe) and quantitatively by: pulmonary artery systolic pressure (PASP), RV fractional area change (RVFAC), RV longitudinal myocardial velocity (RVS'), RV basal diameter, RV free wall longitudinal strain (FWLS) and tricuspid annular plane systolic excursion (TAPSE). RVFAC was determined as abnormal if ≤35%. RVFWLS was calculated as the systolic peak of the average curve from a 6-segment ROI after manually excluding the septal segments [17,18] and defined as normal if ≤−20% [16,19,20]. Stratification according to pre-operative RV function was not possible due to the prevalence of RV dysfunction at baseline.

Degree of valvular regurgitation of the mitral and tricuspid valves were recorded qualitatively as categorical variables (mild, moderate, moderate-severe, severe), and in the case of MR only, quantitatively by: proximal isovelocity surface area (PISA), regurgitation fraction (RF), end regurgitant orifice area (EROA), regurgitant volume and vena contracta (VC).

All 2D-STE measurements were analyzed offline by two experienced independent observers (SH & NB). For assessment of intra- and inter-observer variability, each observer was blinded to the other observer's results. Measurements were repeated after a >4-week interval by the same observers blinded to the initial measurements and reproducibility was comparable with quaternary centers experienced in the technique. 2D-TTE image quality was sufficient to perform volumetric analysis in all 46 patients, but on 41 occasions (41/138; 30% of all TTEs analyzed), the image quality was insufficient or not available to perform full 2D-STE analysis.

2.3. Hemodynamic data

Right heart catheterization (RHC) data were routinely collected pre-operatively and shortly after device deployment by a cardiac anesthetist blinded to TTE image acquisition and interpretation. Collected parameters included right atrial (RA) pressure, PASP, PA diastolic pressure (PADP), mean PA pressure (MPAP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI), stroke volume index (SVI) and RV stroke work index (RVSWI). Overall, 31 of 46 patients (67%) had complete RHC data for full hemodynamic analysis.

For the purpose of this study, we defined improvement in RV function as: (i) an increase in RVWSI post-device deployment; and (ii) an increase in baseline RVFAC pre-discharge and at 3-months.

2.4. Statistical methods

Reporting data was manually entered by an independent observer. All descriptive data are reported as mean ± SD. A repeated-measures analysis was conducted comparing echocardiographic measures across time. After identification of an overall significant difference, all possible pairwise comparisons were made, and a Tukey adjustment was applied to control the overall type I error rate. A Wilcoxon rank-sum analysis was used to examine the difference between time intervals. Data analysis was performed with SPSS-24 (IBM Corporation, Armonk, New York).

Table 1
Pre-operative demographic characteristics of study population.

	(n = 46)
Age (years), mean ± SD	72 ± 9
Height (cm), mean ± SD	171 ± 9
Weight (kg), mean ± SD	77 ± 16
BSA (m^2), mean ± SD	1.9 ± 0.2
Sex	
Male, n (%)	34 (74%)
Female, n (%)	12 (26%)
Race	
White, n (%)	44 (96%)
COPD, n (%)	2 (4%)
Creatinine (μmol/L), mean ± SD	130 ± 59
eGFR (mL/min), mean ± SD	53 ± 20
NT-proBNP (ng/L), mean ± SD	3447 ± 3148
Heart rate (bpm), mean ± SD	74 ± 13
Cardiovascular history	
Atrial fibrillation	38 (83%)
NYHA class 3–4	46 (100%)
Hypertension	32 (70%)
Coronary artery disease	33 (72%)
MR mechanism	
Primary, n (%)	4 (9%)
Secondary/functional, n (%)	42 (91%)
Medications	
ACE inhibitors, n (%)	30 (65%)
Beta-blockers, n (%)	34 (74%)
Digoxin, n (%)	5 (11%)
Diuretics, n (%)	41 (89%)
MRA, n (%)	26 (57%)
ARNI, n (%)	1 (2%)
CRT, n (%)	7 (15%)
Function	
STS-PROM, mean ± SD	11 ± 8
6MWT, mean ± SD	284 ± 138

Abbreviations: ACE = angiotensin converting enzyme; ARNI = angiotensin receptor neprilysin inhibitor; BSA = Body Surface Area using Mosteller formula; CRT = cardiac resynchronization therapy; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal prohormone brain natriuretic peptide; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgery predicted risk of mortality; 6MWT = six-minute walk test.

3. Results

3.1. Baseline characteristics

Forty-six of the 47 (98%) patients who underwent TMVI between October 2014 and October 2019 were enrolled in this analysis. The age of the study population was 72 ± 9 years (74% males; n = 34) (Table 1). All were New York Heart Association (NYHA) functional classes III or IV. All patients had ≥ grade 3 + MR before TMVI and most patients (91%) had secondary/functional MR (predominantly due to ischemic leaflet tethering) (Table 2). In patients with a LVEF 35–50%, 54% had an EROA ≥ 0.4 cm^2, and in patients with a LVEF ≤ 35%, all patients had an EROA ≥ 0.2 cm^2. Baseline demographic and TTE characteristics of the study population are reported in Tables 1 and 2.

3.2. Hemodynamic data

Resting PASP measured invasively immediately before TMVI was elevated (≥25 mmHg) in 29 patients (88%) (PASP 48 ± 16 mmHg; PADP 26 ± 8 mmHg; MPAP 34 ± 8 mmHg). Although there was no change in PA pressures immediately after TMVI (PASP 48 ± 13 mmHg; PADP 27 ± 7 mmHg; MPAP 35 ± 9 mmHg; p = 0.18) (Table 3), there were immediate increases in contractility as evidenced by an increase in RVSWI (from 7 ± 4 g/m/beat/m^2 to 11 ± 5 g/m/beat/m^2, p < 0.001) (Fig. 2), SVI (from

Table 2
Comparison of pre-, post- and short-term TTE characteristics of the study population.

	Pre-	Pre-discharge	1 to 3 months	Pre- to Pre-discharge; Pre- to 3-months
LV function		(n = 46)	(n = 46)	
LV EF ± SD (%)	40 ± 10	35 ± 12	36 ± 15	**p = 0.001; p = 0.008**
LV EDD ± SD (mm)	60 ± 6	60 ± 8	60 ± 8	p = 0.510; p = 0.732
LV ESD ± SD (mm)	46 ± 8	51 ± 10	50 ± 11	**p = 0.001; p = 0.008**
LV EDV ± SD (mL)	166 ± 52	133 ± 44	147 ± 72	**p = 0.001;** p = 0.062
LV ESV ± SD (mL)	103 ± 43	84 ± 32	102 ± 66	**p = 0.021;** p = 0.939
LV EDVI ± SD (mL/m^2)	88 ± 24	72 ± 23	70 ± 40	**p = 0.001; p = 0.003**
LV ESVI ± SD (mL/m^2)	54 ± 20	45 ± 17	48 ± 35	**p = 0.033;** p = 0.328
LV global longitudinal strain (%)	−9.6 ± 3	−9.4 ± 4.4	−8.2 ± 4.7	p = 0.446; p = 0.059
LV circumferential strain (%)	−13.4 ± 5.3	−16.2 ± 8.9	−14.1 ± 6.2	p = 0.586; p = 0.878
LV radial strain (%)	6.5 ± 4.8	5.5 ± 8.9	6.5 ± 9.2	p = 0.443; p = 0.213
Mitral Regurgitation				
Nil-trivial, n (%)	0 (0%)	41 (89%)	42 (91%)	**p < 0.001**
Mild, n (%)	0 (0%)	5 (11%)	4 (9%)	p = N/S
Moderate, n (%)	0 (0%)	0 (0%)	0 (0%)	
Moderate-Severe, n (%)	10 (22%)	0 (0%)	0 (0%)	**p < 0.001**
Severe, n (%)	36 (78%)	0 (0%)	0 (0%)	
Tricuspid Regurgitation				
Nil-Trivial, n (%)	10 (22%)	18 (39%)	18 (39%)	**p < 0.001**
Mild, n (%)	20 (43%)	23 (50%)	23 (50%)	
Moderate n (%)	9 (20%)	0 (0%)	0 (0%)	**p < 0.001**
Moderate-Severe, n (%)	5 (11%)	3 (7%)	1 (2%)	p = N/S
Severe, n (%)	2 (4%)	2 (4%)	4 (9%)	
RV function				
PASP (mmHg) ± SD	49 ± 16	44 ± 17	36 ± 12	**p = 0.025; p < 0.001**
RV FAC (%), mean ± SD	28 ± 7	33 ± 8	35 ± 9	**p < 0.001; p < 0.001**
RV base (cm), mean ± SD	4.2 ± 0.7	4.3 ± 0.8	4.4 ± 0.8	p = 0.460; p = 0.458
RV mid (cm), mean ± SD	3.6 ± 1.0	3.7 ± 0.9	3.6 ± 1.0	p = 0.170; p = 0.438
RV length (cm), mean ± SD	7.4 ± 1.2	6.9 ± 1.4	6.9 ± 1.4	p = 0.133; **p = 0.038**
RV FWLS (%), mean ± SD	−14.2 ± 5.0	−17.8 ± 6.4	−17.6 ± 7.3	**p = 0.047**; p = 0.162
RVS' (cm/S), mean ± SD	7.4 ± 2.6	7.3 ± 2.1	8.2 ± 2.8	p = 0.429; p = 0.067
TAPSE (cm), mean ± SD	1.0 ± 0.3	1.3 ± 0.4	1.5 ± 0.5	p = 0.453; **p = 0.033**

Abbreviations: FAC indicates fractional area change; FWLS indicates free wall longitudinal strain; LV indicates left ventricular; LVEDD indicates left ventricular end diastolic dimension; LVEDV indicates left ventricular end diastolic volume; LVEDVI indicates left ventricular end diastolic volume indexed; LVEF indicates left ventricular ejection fraction; LVESD indicates left ventricular end systolic dimension; LVESV indicates left ventricular end systolic volume; LVESVI indicates left ventricular end systolic volume indexed; MV indicates mitral valve; PASP indicates pulmonary artery systolic pressure; RV indicates right ventricular; TAPSE indicates tricuspid annular plane systolic excursion.

Table 3
Intra-procedural right heart catheterization.

	Pre-Deployment (n = 46)	Post-Deployment (n = 31)	Pre- to Post-Deployment
CVP (mmHg)	15 ± 5.2	16 ± 6	p = 0.47
PASP (mmHg)	48 ± 16	48 ± 13	p = 0.26
PADP (mmHg)	26 ± 8	27 ± 7	p = 0.14
MPAP (mmHg)	34 ± 8	35 ± 9	p = 0.18
CO (L/min)	3.7 ± 1.1	4.6 ± 1.4	**p < 0.001**
CI (L/min/m)	1.9 ± 0.5	2.4 ± 0.7	**p < 0.001**
Stroke volume index (mL/beat/m^2)	29 ± 9	34 ± 11	**p < 0.001**
RVSWI (g/m/beat/m^2)	7 ± 4	11 ± 5	**p < 0.001**
PAPI	1.4 ± 0.8	1.5 ± 0.8	p = 0.20

All values are mean ± standard deviation.
Abbreviations: CI indicates cardiac index; CO indicates cardiac output; CVP indicates central venous pressure; MPAP indicates mean pulmonary artery pressure; PADP indicates pulmonary artery diastolic pressure; PAPI indicates pulmonary artery pulsatility index; PASP indicates pulmonary artery systolic pressure; RVSWI indicates right ventricular stroke work index.

29 ± 8 mL/beat/m^2 to 34 ± 11 mL/beat/m^2, p < 0.001) and CO (from 3.7 ± 1.1 L/min to 4.6 ± 1.4 L/min, p < 0.001) (Table 3). CVP and HR remained steady (Table 3).

3.3. Left ventricular remodeling

MR was abolished in all patients immediately following TMVI and this was associated with a reduction in LV volumes. At 3-months no patient had > 1 + MR (n = 46; p < 0.001 vs baseline) (Table 2; Fig. 3). Thirty-six patients (78%) had a LVEF < 50% at baseline, and 18 patients (39%) had a LVEF ≤ 35%. For the entire group, indexed LVEDV (LVEDVI) and indexed LVESV (LVESVI) were elevated pre-operatively (88 ± 24 mL/m^2 and 54 ± 20 mL/m^2 respectively) (Table 4), and decreased on discharge to 72 ± 23 mL/m^2 (p = 0.001) and 45 ± 17 mL/m^2 (p = 0.03), respectively (Tables 2 and 4; Fig. 4). The improvement in LVEDVI was sustained at 3-month follow-up (70 ± 40 mL/m^2, p = 0.003), but was associated with a small decline in LVEF (40 ± 10% vs 36 ± 15%; p = 0.008) (Table 2). There was a non-significant decline in LVGLS, whilst circumferential and radial strain remained steady at 3-months (Table 2).

3.4. Right ventricular function

RV function was impaired at baseline and improved after TMVI. In keeping with improved RVSWI, RVFAC increased from 28 ± 7% before TMVI to 33 ± 8% at hospital discharge (p = 0.03), and 34 ± 9% at 3-months (p < 0.001 vs baseline) (Table 2; Fig. 2). TAPSE increased from 1.0 ± 0.3 cm before TMVI to 1.5 ± 0.5 cm at 3-months (p = 0.03). RVFWLS improved from −14.2 ± 5.0% before TMVI to −17.6 ± 7.3% at 3-months (p = 0.05), whilst there was a non-significant trend towards improved RVS' (Table 2).

There was a significant reduction in RV length post TMVI (p = 0.04) with an associated reduction in TR severity. At discharge, 41 (89%) patients had no detectable/trivial or mild TR (p < 0.001), an improvement that was sustained at 3-month follow-up (Table 2;

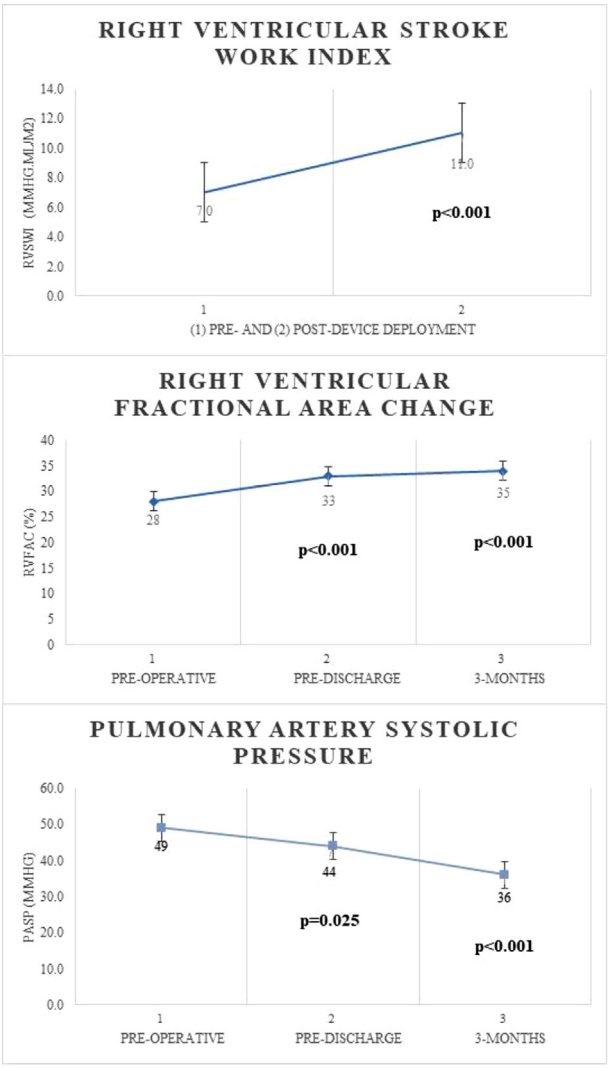

Fig. 2. RV hemodynamics and remodeling. a. Improvement in RVSWI post-device deployment. b. Change in RVFAC from baseline to pre-discharge and 3-months. c. Decrease in pulmonary artery systolic pressure to 3-months. Abbreviations: RVFAC = right ventricular fraction area change; RVSWI = right ventricular stroke work index.

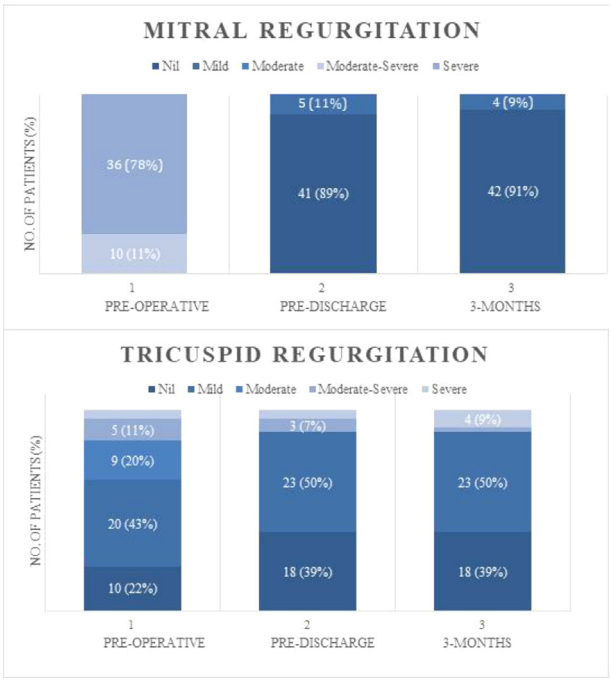

Fig. 3. Comparison of pre- and post- operative MR and TR. (top): Bar chart comparison of pre- and post-operative MR following TMVI. All patients had ≥ 3 + MR pre-operatively. There was a significant reduction in MR pre-discharge ($p < 0.001$) and at 3 months ($p < 0.001$). (bottom): Bar chart comparison of pre- and post-operative TR following TMVI. There was an increase in patients with nil/mild TR post-operatively from 65% to 89% post-operatively and at 3 months ($p < 0.001$). Abbreviations: MR = mitral regurgitation; TMVI = transcatheter mitral valve implantation; TR = tricuspid regurgitation.

Fig. 3). PASP decreased significantly (from 49 ± 16 mmHg to 36 ± 12 mmHg at 3-months; $p < 0.001$) (Table 2; Fig. 2).

3.5. Right ventricular remodeling stratified for left ventricular function

RV dysfunction was prominent in the 18 patients with baseline LVEF < 35%: RVFAC 25 ± 9%; RVFWLS −13 ± 5%; RVS' 6.5 ± 2.1 cm/s; TAPSE 1.3 ± 0.5 cm; PASP 48 ± 14 mmHg) (Table 4). After TMVI, RV function improved at 3-months, with an increase in RVFAC (to 35 ± 11%, $p = 0.03$) and reduction in PASP (to 32 ± 9 mmHg, $p = 0.01$, Table 4). There were non-significant increases in RVFWLS, RVS' and TAPSE (Table 4).

Patients with a LVEF ≥ 35% had less severe RV dysfunction before TMVI compared to patients with a LVEF < 35% (RVFAC 29 ± 5%; RVFWLS −15 ± 5%; RVS' 7.9 ± 2.8 cm/s; TAPSE 1.4 ± 0.4 c m; PASP 47 ± 17 mmHg) (Table 4). In this group, RVFAC also increased to 35 ± 8% ($p = 0.01$) and PASP decreased to 34 ± 12 mmHg ($p = 0.01$) 3-months after TMVI (Table 4). There were non-significant increases in RVFWLS and TAPSE (Table 4).

4. Discussion

The findings of this study, the first to evaluate RV function after TMVI in patients excluded from conventional cardiac surgery due to excessive risk, can be summarized as follows: TMVI using the transapically tethered Tendyne mitral valve system resulted in (i) abolition of MR with an associated immediate increase in SVI and a reduction in LV volumes; (ii) an immediate increase in RVSWI with an improvement in RV contractile performance as measured by RVFAC; (iii) a reduction in PASP and severity of TR at 3-months. The extent of improvement in RV function at 3-months in the group with severe LV dysfunction was similar to that of the group with less severe LV and RV dysfunction at baseline.

4.1. Intrinsic myocardial dysfunction

The volume overload of chronic MR results in progressive eccentric LV hypertrophy and an eventual decline in contractile performance. RV dysfunction in patients with chronic MR is often overlooked but occurs as a consequence of left-sided heart disease. RV dysfunction has previously been shown to occur in approximately 30% of patients referred for MV repair surgery [1–3], and is found in up to 50% of patients with severe MR and LV dysfunction [1–3]. More than three-quarters of patients enrolled in our study had significant RV dysfunction pre-operatively (RVFAC < 35% and RVFWLS ≤ 20%), and of the patients who had detectable TR, all had a PASP ≥ 25 mmHg by echocardiography. The prevalence of pre-operative RV dysfunction has been poorly described in transcatheter treated patients to date [21,22], and is significantly higher in our population than in a previous surgical MV repair series [3]. This finding is unsurprising given that our cohort was deemed too high-risk for conventional mitral valve surgery, but

Table 4
Changes in LV and RV function stratified by baseline LV function.

	Pre-operative	Pre-discharge	1 to 3 months	Pre-operative to Pre-discharge; Pre- to 3-months
A. Severe LV dysfunction (LVEF < 35%) (N = 18)				
LV EF (%)	30 ± 4	29 ± 12	28 ± 12	p = 0.63; p = 0.25
LV EDVI (mL/m^2)	102 ± 23	77 ± 17	90 ± 47	**p < 0.01;** p = 0.32
LV ESVI (mL/m^2)	72 ± 18	54 ± 17	68 ± 42	**p < 0.01;** p = 0.76
LV global longitudinal strain (%)	−9.4 ± 3	−8.5 ± 3	−7.5 ± 6	p = 0.24; p = 0.15
LV circumferential strain (%)	−12 ± 3	−16 ± 9	−14 ± 7	p = 0.70; p = 0.48
LV radial strain (%)	7 ± 3	7 ± 10	7 ± 12	p = 1.0; p = 0.30
Regurgitant orifice area (cm^2)	0.52 ± 0.3	N/A	N/A	N/A
PASP (mmHg)	48 ± 14	39 ± 15	32 ± 9	p = 0.09**; p = 0.01**
RV FAC (%)	25 ± 9	33 ± 10	35 ± 11	**p = 0.02; p = 0.03**
RVFWLS (%)	−13 ± 5	−18 ± 8	−17 ± 7	p = 0.21; p = 0.08
RVS'	6.5 ± 2.1	6.9 ± 2.2	7.2 ± 2.3	p = 1.0; p = 0.46
TAPSE (cm)	1.3 ± 0.5	1.5 ± 0.6	1.5 ± 0.6	p = 0.83; p = 0.17
	Pre-operative	Pre-discharge	1 to 3 months	Pre-operative to Pre-discharge; Pre- to 3-months
B. Moderate LV dysfunction (LVEF ≥ 35%) (N=28)				
LV EF (%)	47 ± 7	39 ± 11	41 ± 14	p=0.62; p=0.25
LV EDVI (mL/m^2)	78 ± 20	70 ± 25	57 ± 28	p=0.06; **p=0.01**
LV ESVI (mL/m^2)	43 ± 12	41 ± 15	36 ± 22	p=0.06; **p=0.01**
LV global longitudinal strain (%)	−10 ± 3	−10 ± 5	−9 ± 3	p=0.74; p=0.18
LV circumferential strain (%)	−15 ± 6	−16 ± 9	−14 ± 6	p=0.84; p=0.75
LV radial strain (%)	6 ± 6	4 ± 8	6 ± 6	p=0.22; p=1.0
Regurgitant orifice area (cm^2)	0.53 ± 0.52	N/A	N/A	N/A
PASP (mmHg)	47 ± 17	46 ± 17	34 ± 12	p=0.22; **p=0.01**
RV FAC (%)	29 ± 5	33 ± 7	35 ± 8	**p=0.01; p=0.01**
RVFWLS (%)	−15 ± 5	−18 ± 7	−18 ± 8	p=0.62; p=0.36
RVS'	7.9 ± 2.8	9.0 ± 3.0	9.0 ± 2.9	p=0.69; p=0.16
TAPSE (cm)	1.4 ± 0.4	1.5 ± 0.4	1.5 ± 0.4	p=0.65; p=0.26

Abbreviations: FAC indicates fractional area change; FWLS indicates free wall longitudinal strain; LV indicates left ventricular; LVEDVI indicates left ventricular end diastolic volume indexed; LVESVI indicates left ventricular end systolic volume indexed; RV indicates right ventricular; LVEF indicates left ventricular ejection fraction; MV indicates mitral valve; N/A = not applicable; PASP indicates pulmonary artery systolic pressure; RV indicates right ventricular; TAPSE indicates tricuspid annular plane systolic excursion; TR indicates tricuspid regurgitation.

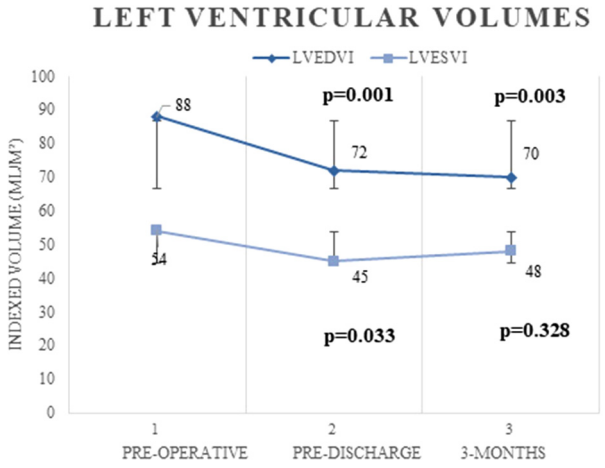

Fig. 4. Comparison of pre- and post-operative LV volumes. Comparison of LVEDVI and LVESVI pre- and post-TMVI. There was an immediate reduction in both values. Abbreviations: LVEDVI = left ventricular end diastolic volume indexed; LVESVI = left ventricular end systolic volume indexed; LV = left ventricular; MR = mitral regurgitation; TMVI = transcatheter mitral valve implantation.

nevertheless highlights the need to monitor for early or late RV dysfunction and/or failure as a consequence of abrupt LV unloading after Tendyne TMVI.

4.2. LV unloading and RV function

LV chamber dilatation, in association with residual or uncorrected MR, increases the pericardial constraints on the right ventricle and impairs RV contractile performance [23]. Following surgical MV repair, a reduction in LV volumes has been associated with an improvement in RV function [3]. Similarly, impaired LA function (as determined by peak atrial longitudinal and/or reservoir strain) has been demonstrated to be significantly impaired in the setting of secondary MR [24], and has emerged as a predictor of overall survival following MV repair surgery [7,8]. As has previously been reported, our data demonstrated that Tendyne TMVI resulted in an abolition of MR and a significant reduction in LV volumes [14,15]. TMVI induced LV unloading was maximal in the period immediately following implantation, however a gradual re-dilatation of the left ventricle was observed in those patients with severe pre-existing LV dysfunction (Table 4; Fig. 4). We also observed a post-operative reduction in LVEF which is consistent with what has previously been described in surgical and transcatheter repair studies due to the unmasking of the true intrinsic myocardial function of the volume-loaded LV through elimination of MR. Regardless, the abolition of MR and concomitant reduction in LV volumes, resulted in an immediate and sustained improvement in RV function as determined invasively post-deployment by RVSWI and non-invasively by RVFAC on echocardiography ($p < 0.001$; Tables 2 and 3; Fig. 2). The improvement in RV function was seen both in patients with moderate ($p = 0.02$) and severe ($p = 0.02$) LV dysfunction. Non-significant changes in RVFWLS and TAPSE when stratified for LVEF, suggest that reduced pericardial constraints, rather than an improvement in intrinsic annular or longitudinal contractility, is the mechanism by which improved RV function occurred.

4.3. Improved LV septal function and RV function

Chronic MR is frequently associated with impaired ventricular septal motion. The contribution of septal contraction to RV systolic

function ranges from 24% in a normal RV to 35% in RV dysfunction [25,26]. Interventricular septal contraction is able to maintain RV function and cardiac output despite RV free-wall impairment [3,25–27]. In this study, LV radial and circumferential strain remained steady at 3-months despite an overall decline in other measurements of LV contractile performance including EF and GLS (Table 2). This observation might suggest a redistribution of LV contractile load from the apex to the base of the heart, possibly related to the mechanical effect of the tether and its fixation to an apical pad. Future evaluation of the effect of the apical tether in altering LV geometry is warranted.

4.4. Indirect consequences of MR correction

RV dysfunction in the setting of MR may be further exacerbated by the presence of TR which occurs due to progressive RV and tricuspid annular dilatation. While the prognostic importance of TR following surgical and transcatheter mitral repair is well known [28], relatively little has been reported on the impact of mitral interventions on severity of TR. In one study of surgical mitral repair for ischemic MR, ≥2 + TR was present in 30% of patients pre-operatively. Post-operatively, there was little change in TR severity, irrespective of whether or not tricuspid annuloplasty had been performed [29]. Conversely, in the COAPT trial [30], at 2-year follow-up, >2 + TR was less frequent in the device group compared with the control group (49.9% vs 81.0%; HR 0.43, 95% CI: 0.25, 0.74). Our study demonstrated a significant reduction in overall TR burden which was sustained to 3-months. Pulmonary hypertension secondary to severe MR is also known to exacerbate RV dysfunction by increasing RV afterload. In our study, there was a progressive reduction in PASP 3-months after TMVI on echocardiography as we might have expected (Table 2).

To date, there is a paucity of data on the acute off-pump ventricular response to TMVI. Our group has previously reported on changes to LV function [14,31], and now present our data on improvements in RV function. Better appreciation of RV physiological responses that occur due to abrupt correction of MR may assist in the prevention of acute decompensated right heart failure in at-risk patients with severe secondary MR undergoing TMVI.

4.5. Study limitations

Our study relied on echocardiographic image quality for assessment of RV systolic function. Sub-optimal image quality or tracking of the endocardial border occurred most commonly pre-discharge, due to the difficulty in obtaining an adequate dedicated RV apical four-chamber view in the presence of a recent left lateral thoracotomy scar and surgical dressings. A cutoff value of −20% for abnormal RVFWLS was used for this study (derived from vendor specific data). We acknowledge that one of the most important and widely discussed limitations of 2D-STE remains inter-vendor variability [32,33]. Nevertheless, our inter- and intra-observer intra-class coefficients were comparable to 2D-STE data from other high-volume centers. Due to protocol constraints, we did not perform cardiovascular magnetic resonance (CMR), LA strain, or three-dimensional TTE RV assessment to confirm and extend our findings, nor did we report quantitative TR analysis as it was not performed consistently across all three study centers. There was insufficient RHC data in 15 patients to perform RVSWI measurement.

5. Conclusions

RV dysfunction is a frequent finding in patients referred for mitral valve surgery and is both a direct and indirect consequence of LV volume overload. Tendyne TMVI resulted in an immediate improvement in RV function, most likely due to abolition of MR with an associated reduction in LV volumes and reduction in PASP. The preservation of circumferential and radial strain despite an abrupt reduction in LV volume loading, raises the possibility that the apical tether redistributes LV contractile forces and enhances the interventricular septal contribution to RV function. Further longitudinal studies of larger cohorts are needed to confirm and extend our results.

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