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Evolution of right ventricular dysfunction and tricuspid regurgitation after TAVI: A prospective study

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ABSTRACT

Background: Right ventricular (RV) dysfunction and tricuspid regurgitation (TR) may impact prognosis of patients undergoing Transcatheter Aortic Valve Implantation (TAVI). We aimed to evaluate the evolution of previous RV dysfunction and/or significant TR after TAVI procedure.

Methods: All patients undergoing TAVI between January 2018 and January 2019 were enrolled in this prospective cohort. Patients with at least one right heart (RH) abnormality at baseline including RV dysfunction (TAPSE < 17 mm, S-wave < 9.5 cm/s, Fractional area change < 35%, Strain > -20%, Tei > 0.54) and/or significant TR (Effective Regurgitant Orifice Area ≥ 40 mm² and/or Regurgitant Volume ≥ 45 mL) underwent transthoracic echocardiography at day 1 and 6-month after TAVI. The primary endpoint was the regression of pre-TAVI RV dysfunction and/or significant TR at 6-month follow-up.

Results: The study enrolled 144 patients including 76 women (52.8%) with a mean age of 81.1 ± 6.8 yo, a mean EuroSCORE 2 of 5.2 ± 3.9%. At least one RH abnormality was observed in 53 patients (36.8%). At 6-month, at least one RV dysfunction parameter significantly improved in 26 patients (63.4%), TAPSE increasing from 13.0 ± 2.6 to 16.0 ± 9.8 mm, $p < 0.0001$ and S-wave from 7.7 ± 1.2 to 10.0 ± 2.6 cm/s, $p = 0.004$. Among 31 patients with baseline significant TR, TR decreased in 14 (45.2%); $p = 0.003$. Among patients with baseline RH abnormalities, 13 (24.5%) fully recovered. Baseline significant TR was predictive of 6-month clinical outcomes (OR = 3.1, 95%CI = [1.01–9.0], $p = 0.03$).

Conclusion: In our recent intermediate surgical risk TAVI population, RV dysfunction and/or significant TR are frequent at baseline and fully or partially recover in most patients at 6-month follow-up.

1. Introduction

Recent extension of Transcatheter aortic valve implantation (TAVI)

indications to intermediate risk patients [1] must be associated with optimal results since surgical aortic valve replacement (SAVR) is associated with excellent results in this population [2]. While right

Abbreviations: AS, Aortic Stenosis; EDA, End-Diastolic Area; EROA, Effective Regurgitant Orifice Area; ESA, End-Systolic Area; EuroSCORE, European System for Cardiac Operative Risk Evaluation; FAC, Fractional Area Change; IVA, Isovolumic Acceleration; LVEF, Left Ventricular Ejection Fraction; PISA, Proximal Isovelocity Surface Area; RH, Right Heart; RV, right ventricular; R Vol, Regurgitant Volume; SAVR, Surgical Aortic Valve Replacement; sPAP, Systolic Pulmonary Arterial Pressure; TAPSE, Tricuspid Annular Plane Systolic Excursion; TAVI, Transcatheter Aortic Valve Implantation; TTE, Transthoracic Echography.

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¹ These authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

ventricular (RV) function, assessed by ring parameters, has been shown to be worsened and associated with poor prognosis after SAVR [3,4], RV function evolution and its prognostic impact after TAVI remain controversial [5–8]. In recent studies, RV dysfunction was frequent at baseline, observed in 1/3 of patients undergoing TAVI and associated with mortality at follow-up [6,7]. The evolution of RV function remained variable according studies, from at least 50% of RV dysfunction correction to stable RV function after TAVI [5–7]. On the other hand, tricuspid regurgitation (TR) is frequent before TAVI (11–27%) with a variable evolution after the procedure [5,8–10]. Significant TR is considered as a poor prognostic factor after TAVI in retrospective studies [11,12] but prospective studies are lacking to confirm these results. Importantly, predicting evolution of TR after TAVI could also impact the decision between TAVI and SAVR, as surgery can correct an associated TR by contrast to TAVI. Lastly, available data on RV dysfunction and TR evolution after TAVI and their prognostic impact include mainly high-risk patients, no longer representative of current TAVI population.

The main objective of this study was to evaluate the 6-month evolution of baseline right heart (RH) abnormality (RV dysfunction AND/OR significant TR) in a prospective cohort of intermediate surgical risk patients undergoing TAVI. The secondary objective was to compare the 6 months clinical outcomes after TAVI, in patients with and without baseline RH abnormality.

2. Methods

2.1. Study population and patient selection

This prospective study included all consecutive patients undergoing TAVI for symptomatic severe aortic stenosis (AS) (aortic valve area < 1 cm² and/or mean aortic gradient < 40 mmHg) between January 2018 and January 2019, in Montpellier and Nîmes University Hospitals, after heart team decision. Exclusion criteria included balloon valvuloplasty before TAVI and TAVI for aortic regurgitation. All patients were given full study information and written consent was collected. The protocol was approved by the local ethics committee and the institutional regulatory authorities (IRB-MTP_2020_04_202000437) and was conducted according to the principles of the Declaration of Helsinki.

2.2. Study design and experimental protocol

A baseline (day-1 or day 0 before TAVI) transthoracic echocardiography (TTE) evaluation was performed by a certified cardiologist trained in TTE in all patients at Montpellier University Hospital, using VIVID or PHILIPS EPIC ultrasound devices. These parameters were systematically assessed: (1) RV function quantification: TAPSE, pulsed tissue Doppler S-wave, RV fractional area change (FAC), Tei index, isovolumic acceleration (IVA), RV free wall 2D strain; (2) TR quantification: severity grades with PISA radius, effective regurgitant orifice area (EROA) and regurgitant volume (R Vol), (Supplemental Fig. 1); (3) left ventricle function (LVEF), left filling pressures (E/A, E/E'), left atria size, mean transaortic gradient and associated valvular disease; (4) right heart (RH) dimensions (right atria dimensions, End-Diastolic Area (EDA), End-Systolic Area (ESA), size of the tricuspid ring) and right pressure (Systolic Pulmonary Arterial Pressure (sPAP), size of the inferior vena cava). RV dysfunction was defined by at least two criteria including TAPSE < 17 mm, S-wave < 9.5 cm/s, Fractional area change < 35%, Strain > -20%, Tei > 0.54 and significant TR as moderate or severe by effective regurgitant orifice area 40 mm² and regurgitant volume 45 mL according to the European Society of Cardiology guidelines [1,13,14]. Patients with RV dysfunction AND/OR moderate to severe TR at baseline were defined as patients with at least one RH abnormality. In these patients, a TTE with the same parameters assessment was performed at day-1 and 6-month after the procedure, by the same physician. In all patients, baseline characteristics, procedural details and in-hospital outcomes were collected from medical records. In patients who were

not scheduled to the 6-month TTE, the clinical follow-up was obtained by phone questionnaire conducted with the patient or with physicians (cardiologist, attending physician).

2.3. TAVI procedure

The TAVI procedure was performed under general or local anesthesia using transfemoral access or alternative access sites (transcarotid, subclavian, transapical, transaortic) in case of unsuitable ilio-femoral anatomy. Both balloon-expandable Edwards SAPIEN 3 (Edwards Lifesciences LLC, Irvine, CA, USA) and self-expandable CoreValve Evolut R (Medtronic, Inc., Minneapolis, Minnesota) devices were implanted according to operators' choice. Rapid pacing (160–200/min) was performed only for balloon-expandable prosthesis implantation. A final control of the implanted device was performed by aortography and TTE for all patients. Patients were referred to intensive care unit or general cardiology ward according to predefined criteria [15].

2.4. Study endpoints

The primary endpoint was the regression of at least one RH abnormality (RV dysfunction criteria and/or significant TR) after TAVI assessed by TTE at 6-month follow-up.

We described in-hospital complications (death, stroke, major bleeding and vascular complications, myocardial infarction, heart failure, acute kidney injury and new conductive disorders requiring pacemaker implantation) according to VARC-2 criteria [16]. The secondary endpoint was a composite of 6-month all-cause mortality, stroke, major bleeding and vascular complications, myocardial infarction, heart failure, acute kidney injury and rehospitalization for cardiac cause [16].

2.5. Statistical analysis

Patient's characteristics were presented using mean \pm standard deviation (SD) for continuous variables and frequencies and proportions for categorical variables. According to RH abnormality, patients were compared using the student's *t*-test or the Wilcoxon-Mann-Whitney test for continuous variables and the chi-square or Fisher's test for categorical ones. The evolution of quantitative parameters of RV dysfunction was assessed using paired *t*-tests, and the evolution of TR was assessed using McNemar's Chi-square tests. The evolution of each parameter was assessed in patients with RH abnormality at baseline. According to the secondary outcome, patients were compared using the Wilcoxon-Mann-Whitney test for continuous variables and the chi-square or Fisher's test for categorical ones. Variables with a univariate *p*-value < 0.2 were included in a multivariable logistic regression, and then selected using a stepwise method. For all analyses, a *p*-value < 0.05 was considered significant. Statistics were performed with SAS 9.4 (SAS Institute, Cary, North Carolina).

3. Results

3.1. Population baseline characteristics

Among 150 patients undergoing TAVI during the study period, 144 patients were included in the analysis. Study Flow chart is presented in Fig. 1. The mean age was 81.1 ± 6.8 y and 76 patients (52.8%) were female. Baseline characteristics are summarized in Tables 1 and 2.

A transfemoral access was performed in 124 patients (86.1%) and a transcarotid approach in 20 patients (13.9%). An Edwards Sapien 3 valve was implanted in 86 patients (59.7%) and a Corevalve Evolut R in 58 patients (40.3%).

3.2. Baseline RH abnormalities

At baseline, 53 patients (36.8%) had at least one RH abnormality and

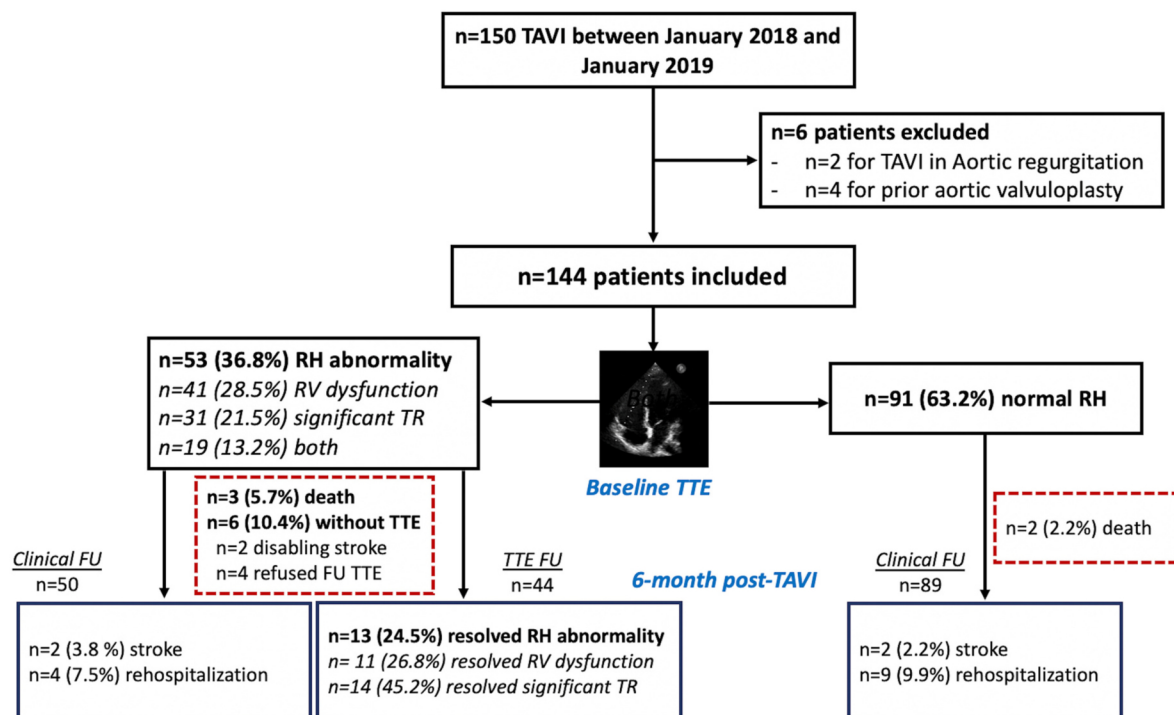


Fig. 1. Study flow chart, RH abnormalities evolution and clinical outcomes.

19 (13.2%) had both RV dysfunction and significant TR, Fig. 1. In patients with baseline RV dysfunction ($n = 41$, 28.5%), TAPSE was abnormal in 29 patients (20.1%), S-wave in 23 patients (16.0%), RV Strain in 16 patients (11.1%), FAC in 12 patients (8.3%) and Tei index in 9 patients (6.3%). A total of 31 patients (75.6%) had RV dysfunction based on 2 parameters, 9 (22.0%) based on 3 parameters and 1 based on 4 parameters (2.4%).

At baseline, 31 patients (21.5%) had significant TR, moderate in 27 patients (18.8%) and severe in 4 patients (2.8%). In comparison with patients without RH abnormality, patients with RH abnormality had a higher EuroSCORE 2 ($6.2 \pm 4.5\%$ vs. $4.7 \pm 3.4\%$, $p = 0.02$), had more frequently prior cardiac surgery ($p = 0.01$), atrial fibrillation ($p < 0.01$), a lower LVEF ($p = 0.01$) and higher LV and RV filling pressure Tables 1 and 2.

3.3. Primary endpoint: RH abnormalities evolution

At day 1, no significant evolution of RV dysfunction was observed. TAPSE and S-wave were stable, from 13.0 ± 2.6 to 13.8 ± 3.8 mm ($p = 0.3$) and from 7.7 ± 1.2 to 8.6 ± 2.6 cm/s ($p = 0.09$), respectively.

At 6-month follow-up, 13 patients with RH abnormalities at baseline (24.5%) fully recovered normal RH function (normal RV function and no TR) (Fig. 1), and 33 (62.3%) recovered on at least one RH abnormality parameter. At least two RV function parameters improved in 26 patients (63.4%) with baseline RV dysfunction, with a significant improvement of TAPSE, increasing from 13.0 ± 2.6 to 16.0 ± 9.8 mm, $p < 0.0001$ (Fig. 2A) and S-wave from 7.7 ± 1.2 to 10.0 ± 2.6 cm/s, $p = 0.004$ (Fig. 2B). Evolution of different echocardiographic parameters of RV function at 6-month is detailed in Supplemental Table 1. Among the 41 patients with RV dysfunction at baseline, RV dysfunction completely resolved in 11 patients, (26.8%, $p = 0.01$).

Moderate to severe TR decreased in 5 patients (16.1%) at D1 ($p = 0.7$) and in 14 patients (45.2%) at 6-month ($p = 0.003$), moderate TR becoming < mild ($n = 12$), and severe TR becoming mild ($n = 1$) or moderate ($n = 1$). Effective regurgitant orifice area and regurgitant volume both decreased at 6-month follow-up without reaching significance. Evolution of quantitative parameters of TR are presented in

Supplemental Table 1. TR maximal velocity decreased from 3.2 ± 0.5 m/s to 2.9 ± 0.4 m/s at 6-month, $p = 0.02$.

3.4. Secondary endpoints: in-hospital and 6-month clinical outcomes

In the total population, no patient died within the first 24-h after TAVI. In-hospital complications were major bleeding ($n = 7$, 4.9%), major vascular complications ($n = 5$, 3.5%), acute kidney injury ($n = 5$, 3.5%) and new conductive disorders ($n = 60$, 41.7%) including 32 (22.2%) pacemaker implantations without significant difference between patients with and without baseline RH abnormalities (Supplemental Table 2).

At 6-month follow-up, 5 patients had died (3.5%), 4 had a stroke (2.8%) and 13 (9.0%) were rehospitalized for cardiac cause, without significant difference between patients with and without baseline RH abnormalities (Fig. 1, Supplemental Table 2). Overall, 21 patients out of 144 (14.6%) presented the composite clinical outcome.

In multivariate analysis, only significant TR at baseline (moderate or severe) was predictive of composite clinical outcome at 6-month follow-up (OR = 3.1, 95%CI = [1.01–9.0], $p = 0.03$), independently of age which was the only confounding factor.

Comparing patients with persistent significant TR versus resolved TR, no difference in terms of the composite outcomes was highlighted at 6-month follow-up ($n = 6$ (35.3%) versus $n = 2$ (14.3%) respectively; $p = 0.2$).

4. Discussion

This study evaluated prospectively the evolution of RV dysfunction and/or significant TR in a recent all comers population of patients undergoing TAVI with 3 main findings:

- (1) RH abnormality (RV dysfunction and/or significant TR) was observed in more than 1/3 of patients before TAVI with a higher risk profile in this population;

Table 1

Baseline characteristics of the overall population and according to RH abnormalities.

	Total population n = 144	RH abnormalities n = 53	No RH abnormalities n = 91	p
Age (years)	81.1 ± 6.8	81.3 ± 5.8	80.9 ± 7.4	0.8
Gender (male)	68 (47.2)	31 (58.5)	37 (40.7)	0.04
Euroscore (%)	5.2 ± 3.9	6.2 ± 4.5	4.7 ± 3.4	0.02
STS score (%)	4.2 ± 3.1	4.8 ± 3.9	3.9 ± 2.6	0.3
STS score ≥ 8%	14 (9.7)	6 (11.3)	8 (8.8)	
STS score 4–8%	41 (28.5)	16 (30.2)	25 (27.5)	
STS score < 4%	89 (61.8)	31 (58.5)	58 (63.7)	
NYHA III-IV	90 (62.9)	37 (69.8)	53 (58.9)	0.2
Hypertension	94 (65.3)	33 (62.3)	61 (67.0)	0.6
Diabetes	50 (34.7)	21 (39.6)	29 (31.9)	0.4
Smoker status	25 (18.2)	12 (24.5)	13 (14.8)	0.2
Prior cardiac surgery	9 (6.3)	7 (13.2)	2 (2.2)	0.01
Prior aortic prosthesis	6 (4.2)	4 (7.5)	2 (2.2)	0.19
COPD	23 (16.0)	12 (22.6)	11 (12.1)	0.10
Stroke history	13 (9.0)	5 (9.4)	8 (8.8)	1.00
Ischemic heart disease	51 (35.4)	24 (45.3)	27 (29.7)	0.06
Peripheral arterial disease	10 (6.9)	5 (9.4)	5 (5.5)	0.50
Atrial fibrillation	51 (35.4)	31 (58.5)	20 (22.0)	< 0.01
Aortic bicuspid valve	8 (6.6)	2 (4.9)	6 (7.5)	0.72
Pacemaker	22 (15.3)	10 (18.9)	12 (13.2)	0.36
VKA	47 (32.6)	30 (56.6)	17 (18.7)	< 0.01
Anti-platelet agents	89 (61.8)	30 (56.6)	59 (64.8)	0.33
Creatinine >200umol/L	10 (6.9)	5 (9.4)	5 (5.5)	0.50
Hemoglobin <10 g/dL	4 (2.8)	1 (1.9)	3 (3.3)	1.00
CRP > 10 mg/L	39 (27.1)	19 (35.8)	20 (22.0)	0.07

Values are mean ± SD or n, %.

COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein NYHA: New York heart association; RH: Right heart; STS: Society of thoracic surgeons; VKA: Vitamin K antagonist.

- (2) In patients with baseline RH abnormalities, both RV dysfunction and significant TR significantly improved within 6 months following the TAVI procedure;
- (3) Baseline significant TR was associated with 6-month adverse outcomes.

4.1. RH abnormalities at baseline

In our study, RV dysfunction and/or significant TR before TAVI remained frequent despite a decreasing surgical risk profile in our current TAVI population. Indeed, a RH abnormality was observed in around 1/3 of patients, with 1/4 of RV dysfunction, 1/5 of moderate to severe TR and 10% of both. These results are consistent with the literature [8,12]. Indeed, in the study of Itio et al. [17], RV dysfunction was present in 29% of patients and TR in 19% of patients undergoing TAVI. In our population, RV dysfunction, mainly highlighted by TAPSE and S wave parameters abnormalities, may be more related to overload conditions rather than intrinsic RV dysfunction where RV strain would be more sensitive [18].

On the other hand, TR and RV dysfunction were associated, in around 10% of cases. This finding is also consistent with the study of Asami et al. [6] where 28.8% of patients with RV dysfunction had severe TR. Indeed, left ventricular chronic pressure overload in patients with

Table 2

Echographic baseline characteristics of the overall population and according to RH abnormalities.

	Total population n = 144	RH abnormalities n = 53	No RH abnormalities n = 91	p
LVEF (%)	58.0 ± 11.3	54.5 ± 12.7	60.0 ± 9.9	< 0.01
Mean aortic gradient (mmHg)	49.6 ± 13.8	43.8 ± 10.7	53.0 ± 14.4	< 0.01
Aortic area (cm ²)	0.7 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.04
E/A	0.9 ± 0.5	1.2 ± 0.7	0.8 ± 0.3	0.04
E/E'	12.7 ± 4.2	14.0 ± 3.9	12.0 ± 4.2	0.04
TAPSE (mm)	20.8 ± 5.5	17.5 ± 5.9	22.8 ± 4.1	< 0.01
S wave (cm/s)	11.4 ± 2.6	10.1 ± 2.7	12.3 ± 2.1	< 0.01
IVA (m/s ²)	3.1 ± 1.0	3.1 ± 1.2	3.1 ± 1.0	0.9
FAC (%)	47.0 ± 12.2	41.4 ± 13.8	51.2 ± 8.9	< 0.01
EDA (cm ²)	15.3 ± 7.2	18.1 ± 9.0	13.0 ± 4.2	0.02
ESA (cm ²)	8.2 ± 5.6	10.6 ± 7.1	6.1 ± 2.6	< 0.01
Tei index	0.3 ± 0.2	0.4 ± 0.3	0.2 ± 0.1	< 0.01
RV Strain (absolute value)	22.9 ± 7.7	18.4 ± 8.1	26.9 ± 4.5	< 0.01
sPAP (mmHg)	40.1 ± 13.3	46.0 ± 14.3	35.1 ± 10.1	< 0.01
TR Vmax (m/s)	2.9 ± 0.5	3.1 ± 0.5	2.7 ± 0.4	< 0.01
Branch block	47 (32.6)	18 (34.0)	29 (31.9)	0.8
Mitral leak ≥ moderate	36 (26.5)	11 (22.0)	25 (29.1)	0.4
Aortic leak ≥ moderate	39 (27.7)	18 (34.0)	21 (23.9)	0.2

Values are mean ± SD or n, %.

EDA: End Diastolic Area; ESA: End Systolic Area; FAC: Fractional Area Change; IVA: Iso Volumic Acceleration; LVEF: Left Ventricular Ejection Fraction; RH: Right Heart; RV: Right Ventricular; sPAP: Systolic Pulmonary Arterial Pressure; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR: Tricuspid Regurgitation.

severe AS may be transmitted to RH and be responsible for right ventricle dilatation and dysfunction [6]. In our study, patients with RV dysfunction had a higher EuroSCORE, lower LVEF and more frequent underlying rhythmic cardiopathy [6]. These findings were also observed in the study of Asami et al. [6] showing higher rate of comorbidities (higher EuroSCORE, lower LVEF and higher rate of AF) in patients with RV dysfunction detected before TAVI.

4.2. RH abnormalities evolution

In our study, despite a trend in favor of RH parameters improvement from day 1, this improvement became significant only at 6-month follow-up, in the opposite to previous studies [5,7,8]. Indeed, in the study of Ayhan et al. [5], TAPSE increased from 16.8 ± 0.3 to 17.9 ± 0.3 at day 1 and to 18.7 ± 0.2 mm at 6-month, $p < 0.001$. These differences may be explained by a different population with a sub-normal RV function in this study by contrast to our study where RV dysfunction was more severe. Indeed, RV function improvement may be delayed in patients with worse RV dysfunction at baseline. This progressive RV improvement and decrease of TR velocity can be explained by a progressive RH remodeling after lowering of volumes after obstacle removal. The presence of important TR before TAVI may also minimize the RV dysfunction before the procedure and underestimate the intrinsic RV function improvement after TAVI. Thus, RV function significantly improved 6-month after TAVI, regarding the ring contraction parameters (TAPSE, S-wave), the same markers that tend to deteriorate after

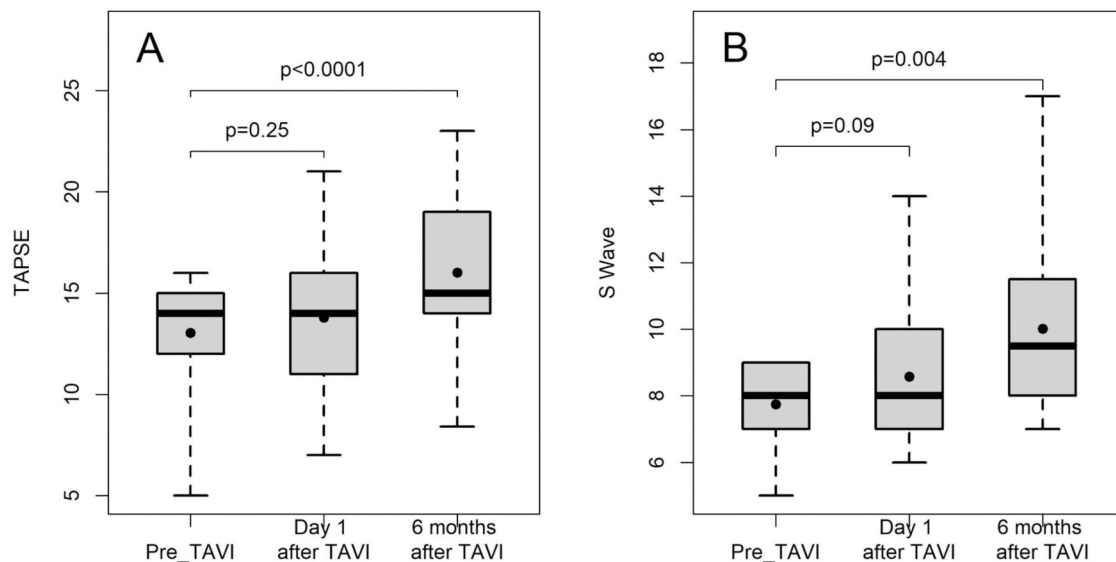


Fig. 2. Evolution of RV dysfunction at 6-month follow-up.

A/ Evolution of TAPSE from baseline to 6-month follow-up, in patients with TAPSE < 17 at baseline; B/ Evolution of S-wave from baseline to 6-month follow-up, in patients with S-wave < 9.5 at baseline.

Boxes and whiskers represent min, Q1, median, Q3, max; points represent the mean.

p-values are Wilcoxon's rank sum test for paired data.

SAVR [8,9]. However, evolution of others than ring RV function parameters after TAVI is still not fully elucidated and further investigations are necessary, these parameters appearing stable after surgery [19]. In our study, around half of moderate to severe TR became minimal to mild after TAVI, this improvement beginning from day 1. Therefore, previous significant TR in patients with AS may probably not be an argument in favor of SAVR as TR may improve in the majority of cases after TAVI. While no significant predictive factor of persistent significant TR was found in our study, Yoshida et al. [20] showed that AF and tricuspid annular dilatation were independent predictors of persistent TR after TAVI.

4.3. Prognostic impact of RH abnormalities

In our study, significant TR at baseline was predictive of 6-month events. These findings are consistent with the meta-analysis of Takagi et al. [21] where significant TR was associated with an approximately 2-fold increase in both early and midterm all-cause mortality in patients undergoing TAVI.

Regarding the prognostic impact of RV dysfunction, a recent study showed an association between RV dysfunction and 1-year all-cause mortality [6]. Moreover, in the meta-analysis of Ren et al. [7], including 4016 patients, RV dysfunction was associated with a significant 78% relative risk increase of mortality at 1-year. However, this association was not highlighted in the subanalysis of the PARTNER II trial without significant association between RV dysfunction and 1-year mortality [3]. In our study, baseline RV dysfunction was not predictive of outcomes at 6-month follow-up. These conflicting results may be explained by different RV dysfunction definitions and a shorter follow-up with a low incidence of events in our study.

4.4. Study limits

This study is limited by its observational nature. Moreover, each echocardiographic parameter has its own limits and TTE could have been performed by different sonographers and/or with two different ultrasound devices, resulting in bias. Third, despite a 12-month period of inclusion, clinical events were infrequent and our study was underpowered to assess the impact of RV dysfunction and significant TR on

mortality. Finally, a few patients had died prior the echocardiographic follow-up, which might have induced a selection bias.

5. Conclusion

In our recent intermediate surgical risk TAVI population, more than 1/3 of patients had RV dysfunction AND/OR significant TR at baseline. In this subgroup of patients, improvement of these parameters is observed in most of them and fully recovering occurred in 1/4 of them at 6-month follow-up. These results argue for volume-dependent related and not intrinsic RH dysfunction before TAVI and do not argue to SAVR to simultaneously correct associated TR. Whether these improvements are related to mortality or clinical events should be evaluated in a larger and long-term follow-up study.

Declaration of Competing Interest

F. Leclercq received research grants from Edwards, Medtronic, Boehringer; consultant fees from Boehringer; and lecture fees from AstraZeneca and Bayer.

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M. Akodad received research grants from Fédération Française de Cardiologie, MUSE-Explore, Biotronik and Medtronic.

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