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To cite this article: Mihai Strachinaru, Ben Ren, Bas M. van Dalen, Nicolas Van Mieghem, Peter P. T. De Jaegere, Lennart van Gils, Tjebbe W. Galema & Marcel L. Geleijnse (2020): Determinants of changes in pulmonary artery pressure in patients with severe aortic stenosis treated by transcatheter aortic valve implantation, Acta Cardiologica, DOI: [10.1080/00015385.2019.1708599](https://doi.org/10.1080/00015385.2019.1708599)

To link to this article: <https://doi.org/10.1080/00015385.2019.1708599>



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Published online: 10 Jan 2020.



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Department of Cardiology, Thorax Center, Erasmus MC, Rotterdam, The Netherlands

ABSTRACT

Background: Elevated pulmonary artery pressure (PAP) in patients with severe aortic stenosis (AS) is a strong predictor of adverse prognosis. This study sought to assess the relation between PAP and clinical and echocardiographic parameters in elderly patients with severe AS, as well as to identify the determinants of the change in PAP after transcatheter aortic valve implantation (TAVI).

Methods: The study included 170 subjects (age 81 ± 7 years, 45% men) with symptomatic severe AS who were treated by TAVI. They underwent a clinical evaluation and a transthoracic echocardiography before the TAVI procedure and 6 months after.

Results: In a multivariable analysis, the independent predictors for baseline PAP were the body mass index (BMI) ($\beta = 0.21$, $p = .006$), COPD GOLD class ($\beta = 0.20$; $p = .009$), the E/e' ratio ($\beta = 0.20$; $p = .02$) and the degree of aortic regurgitation ($\beta = 0.20$; $p = .01$). After TAVI, there was significantly less (51% vs. 29%, $p < .0001$) pulmonary hypertension, defined as a tricuspid regurgitation velocity ≥ 2.8 m/s. The baseline variables related to an improvement in PAP were the tricuspid regurgitation velocity ($p = .0001$) and the E/e' ($p = .005$). From the parameters potentially modified with TAVI, the only independent predictor of PAP variation was the change in the E/e' ratio ($\beta = 0.23$; $p = .01$).

Conclusions: Independent predictors for baseline PAP in elderly patients with symptomatic AS were the BMI, GOLD class, the aortic regurgitation and the E/e' ratio. The baseline predictors for a change in PAP 6 months after TAVI were the baseline PAP and E/e' , with only the change in the E/e' ratio being correlated to the change in PAP.

ARTICLE HISTORY

Received 10 October 2019
Revised 5 December 2019
Accepted 19 December 2019

KEYWORDS

Pulmonary artery pressure; TAVI; E/e' ratio; diastolic dysfunction

Introduction

Aortic stenosis (AS) is the most common valvular heart disease in the Western world and its prevalence is expected to increase due to the aging of the population [1]. The rise in pulmonary artery pressure (PAP) in these patients has been clearly demonstrated as a strong predictor of worse prognosis after medical, surgical or interventional management [2–4]. We also know from several studies that PAP improves after relieving the valvular obstacle [5–7]. There is however little data concerning the determinants of this rise in PAP and in particular on the factors associated with post interventional improvement in PAP [8–12]. This study sought to assess the relation between PAP and clinical and echocardiographic parameters in patients with severe AS, as well as to identify the determinants of improvement in PAP after transcatheter aortic valve implantation (TAVI).

Methods

The study design was monocentric and retrospective, involving patients treated by TAVI for severe AS between 2005 and 2014 in our institution. The study was conducted according to the principles of the Declaration of Helsinki. Retrospective clinical studies are waived for approval by our Institutional Ethical Committee. All patients have given written consent for the use of their anonymised data in this research.

Patient population

After exclusion of patients with prior aortic or mitral valvular surgery, mitral stenosis or significant areas of focal LV akinesia (defined as an akinetic region extending to at least three segments, involving the basal septum and/or the basal lateral wall), the study included 170 subjects (mean age 81 ± 78 years, 45%

CONTACT Mihai Strachinaru  m.strachinaru@erasmusmc.nl  Department of Cardiology, Erasmus MC, Room Rg 427, PB 2040, 3000 CA Rotterdam, The Netherlands

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Table 1. Baseline characteristics of the study patients.

Variable	Study population <i>n</i> = 170
Age	81 (±7)
Male gender	76 (45%)
BMI > 30 kg/m ²	31 (18%)
Diabetes	40 (24%)
Hypertension	91 (54%)
Severe renal dysfunction	19 (11%)
Atrial fibrillation	34 (20%)
Pacemaker before TAVI	15 (9%)
LBBB before TAVI	29 (17%)
Coronary artery disease	92 (54%)
Previous CABG	38 (22%)
Previous PCI	38 (22%)
PCI along with TAVI	19 (11%)
COPD GOLD 2-4	49 (29%)
Pulmonary hypertension	86 (51%)
NYHA class I	10 (6%)
NYHA class II	53 (31%)
NYHA class III-IV	102 (60%)
Log ₁₀ NT-proBNP	2.3 ± 0.6
Angina	47 (27%)
Syncope	15 (9%)

BMI: body mass index; CABG: coronary artery by-pass graft surgery; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease classification of COPD; LBBB: left bundle branch block; NYHA class: New York Heart Association classification of heart failure symptoms; PCI: percutaneous coronary intervention; NT-proBNP: N-terminal pro brain natriuretic peptide.

Data are presented as mean ± SD or number (percentage %).

men) with symptomatic severe AS, defined as an aortic valve area less than 1 cm² and/or less than 0.6 cm²/m² and/or a mean pressure gradient over 40 mmHg, who were treated by TAVI. All patients underwent a clinical evaluation and a transthoracic echocardiography at baseline before the TAVI procedure and at 6 months post-TAVI.

Venous blood samples were drawn from each patient within 30 min of the Doppler echocardiography study after 30 min of supine rest. For NT-proBNP determination, an electrochemiluminescence immunoassay (ProBNP Elecsys, Roche Diagnostics GmbH, Mannheim, Germany) was used. Due to the very large range of values of the natriuretic peptide and the abnormal distribution of this variable, the log₁₀ of the NT proBNP was used in the analysis.

Transthoracic echocardiography

Two-dimensional echocardiography was performed using a Philips iE33 system (Philips, Best, The Netherlands) with the patient in the left lateral decubitus position. Echocardiographic studies were performed by an independent experienced echocardiographer, blinded to the patient's clinical status. All echocardiograms were saved as video loops or still frames in a digital database and were reanalysed by an experienced cardiologist (MS). LV ejection fraction was calculated using the biplane modified

Simpson rule. The mitral inflow velocity profile (*E/A* wave ratio, *E* wave deceleration time) was assessed with pulsed-wave Doppler. The early diastolic velocities at the septal annulus level were assessed with pulse-wave tissue Doppler from a standard apical four-chamber view [13]. Pulmonary artery pressure was estimated from the trans-tricuspid systolic gradient. Tricuspid annular systolic excursion (TAPSE) was measured in standard apical four-chamber view.

Each echocardiographic measurement was performed by at least two different observers: one initial by the sonographer performing the study, validated by a supervising imaging cardiologist; and a second measurement performed by MS (highly experienced imaging cardiologist), who was blinded to the clinical status of the subjects during these measurements. In case of disagreement between the two observers, a highly experienced imaging cardiologist (MG) acted as third observer and adjusted the result.

Definitions

Obesity was defined as a body mass index (BMI) above 30 kg/m² [14]. COPD was classified according to GOLD class [15]. Severe impairment of the renal function was defined as GFR less than 30 ml/min/1.73 m², present for more than 3 months, as estimated by the 2009 CKD-EPI creatinine equation [16]. Aortic and mitral regurgitations were assessed semiquantitatively according to current guidelines for the evaluation of native valves [17]. Pulmonary hypertension (PHT) was considered at a value of the trans-tricuspid systolic gradient above 2.8 m/s [18]. Significant coronary artery disease was defined as >50% stenosis in at least one coronary artery.

Statistical analysis

Continuous variables are presented as means (±SD) if normally distributed. Categorical variables are presented as frequencies and percentages. Differences between continuous variables were assessed by the paired-samples *t* test and between categorical variables by chi-square test. Univariate linear regression was used to identify the factors related to PAP level. The factors found to be significant in univariate analysis or considered relevant based on clinical data were entered into a multivariable linear regression model. The overall performance of the regression model was assessed using *R*² statistics. Collinearity diagnostics and Durbin-Watson's statistics were used to check the assumptions of no multicollinearity and

Table 2. Baseline determinants of PHT.

Parameter	Mean \pm SD	Univariate analysis		Multivariable analysis	
		Beta	<i>p</i>	Beta	<i>p</i>
Age	81 \pm 7	-0.14	.08		
Male gender		-0.08	.28		
BMI	26 \pm 5	0.09	.26	0.21	.006
COPD GOLD class (0–4)	0.78 \pm 0.99	0.19	.01	0.20	.009
Mitral regurgitation (0–3)	1.09 \pm 0.65	0.15	.05	0.10	.21
Aortic regurgitation (0–3)	0.91 \pm 0.69	0.23	.003	0.20	.01
Mean transaortic gradient (mmHg)	44 \pm 15	0.09	.23	0.11	.20
Ejection fraction (%)	55 \pm 12	-0.21	.006	-0.15	.10
<i>E/e'</i> septal	21 \pm 9	0.28	<.0001	0.20	.02
TAPSE baseline (mm)	20 \pm 5	-0.067	.39		
Atrial fibrillation		0.12	.11		
LBBB at baseline		0.10	.19		
Pacemaker at baseline		0.01	.86		
Coronary artery disease		-0.03	.66		
Sever renal failure		-0.13	.11		
Diabetes		0.06	.42		
Hypertension		-0.02	.77		

BMI: body mass index; CI: confidence intervals; COPD: chronic obstructive pulmonary disease; LBBB: left bundle branch block; TAPSE: tricuspid annular plane systolic excursion; SD: standard deviation.

Data are presented as mean \pm SD. Significant *p* values (<.05) are highlighted in bold.

serial independence of errors. A two-sided *p* value less than .05 was used for declaring statistical significance. All statistical analyses were performed with SPSS 21.0 software (SPSS Inc, Chicago, IL).

Results

The baseline characteristics of the population are shown in Table 1. All patients were symptomatic. Ten patients (6%) were in NYHA class I, 53 patients (31%) were in NYHA class II and 102 patients (60%) were in NYHA class III or IV (in five patients NYHA class could not be determined due to immobility). Forty-six patients (27%) had angina and 15 (9%) syncope. Significant COPD (class 2–4) was present in 49 patients (29%), obesity in 32 (18%), severe renal dysfunction in 19 (11%). Ninety-two of these patients (54%) had coronary artery disease, in 38 (22%) already treated by coronary bypass surgery and in 38 (22%) by a percutaneous intervention. In addition, a percutaneous intervention was performed along with the TAVI intervention in 19 (11%) patients. PHT was present in 86 patients (51%). A pacemaker was already present before the TAVI procedure in 15 (9%) and a complete left bundle branch block (LBBB) was diagnosed at baseline in 29 (17%).

Determinants of PHT at baseline

In univariate analysis, COPD class, mitral and aortic insufficiency, ejection fraction and *E/e'* ratio (Table 2, Figure 1) were related to baseline PAP. In a multivariable analysis, the independent predictors for PHT were BMI (Beta = 0.21; *p* = .006), COPD GOLD class (Beta =

0.20; *p* = .009), aortic regurgitation (Beta = 0.20; *p* = .01) and the *E/e'* ratio (Beta = 0.20; *p* = .02).

Baseline predictors of improvement in pulmonary artery pressure

Before TAVI, 86 patients (51%) had PHT (Table 3). After TAVI an improvement in PAP, defined as a decrease in trans-tricuspid systolic gradient as compared to the baseline value, was noted in 101 patients (59%). No improvement or increased gradient was noted in 69 (41%). After TAVI, the number of PHT patients was significantly lower (50; *p* < .0001) and 36 (21%) PHT patients normalised the PAP.

When comparing the baseline parameters in the group with improved trans-tricuspid gradient versus the group without improvement, the only significantly different variables are the baseline value of the trans-tricuspid gradient and the *E/e'* ratio (Figure 2).

Variation of clinical and echographic parameters 6 months after TAVI

There was a significant decrease in NYHA class, mean transaortic gradient, as well as in tricuspid regurgitation velocity (Table 4). We noted a significant decrease in Log₁₀NT-proBNP from 2.3 \pm 0.6 at baseline to 2.1 \pm 0.5 six months after TAVI (*p* = .002). There was no significant change in the mean degree of mitral and aortic regurgitation. The *E* and *A* wave velocity increased significantly, without improvement of mean ejection fraction or *E/e'* ratio.

A new-onset (not present at baseline) LBBB was noticed in 67 (39%) patients. Implantation of a new

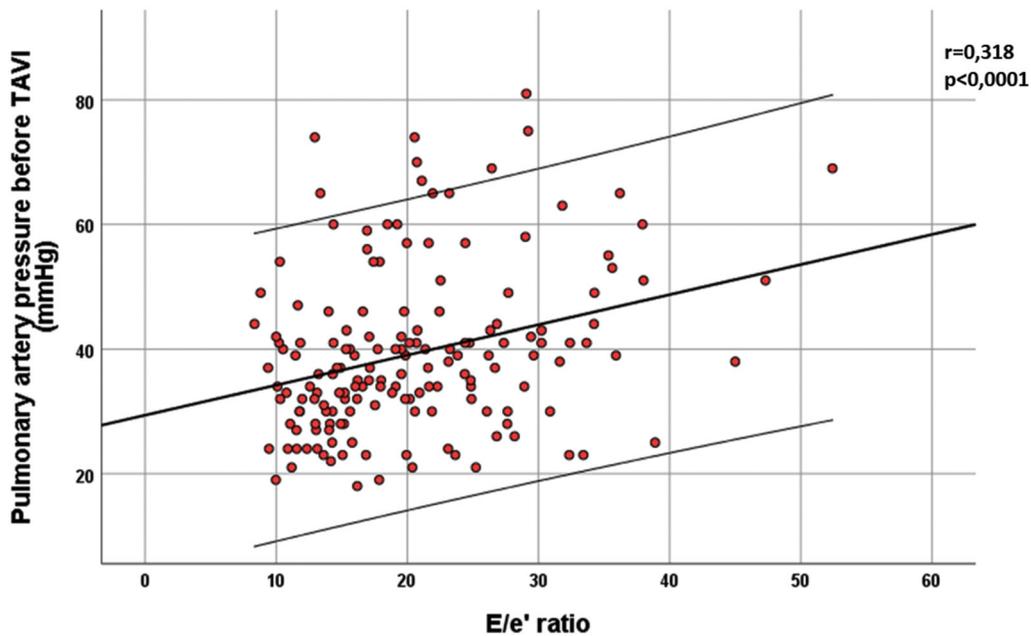


Figure 1. Correlation plot between baseline values of the E/e' ratio and the value of the pulmonary artery pressure as derived from the maximal transtricuspid gradient. A correlation line was fitted to the data (central thick line), as well as 95% confidence intervals (thin lateral lines).

Table 3. Comparison between no improvement or worsening PAP vs. improved PAP.

Variable	No improvement N = 69	Improved N = 101	p
Age	80 ± 8	82 ± 6	.06
Male gender	34 (49%)	42 (42%)	.32
BMI > 30 kg/m ²	12 (17%)	20 (20%)	.15
Diabetes	16 (23%)	24 (24%)	.9
Hypertension	37 (54%)	54 (54%)	.98
Severe renal dysfunction	9 (13%)	10 (10%)	.52
Atrial fibrillation	16 (23%)	18 (18%)	.39
Coronary artery disease	36 (52%)	56 (55%)	.67
PCI along with TAVI	5 (7%)	14 (14%)	.17
COPD GOLD 2–4	19 (28%)	30 (30%)	.76
NYHA class I	3 (4%)	7 (7%)	.48
NYHA class II	27 (39%)	26 (26%)	.06
NYHA class III–IV	37 (54%)	65 (64%)	.16
LVEDP	19 ± 7	19 ± 7	1
COPD GOLD class (0–4)	0.71 ± 1	0.82 ± 1	.48
Mitral regurgitation (0–3)	1.1 ± 0.6	1.1 ± 0.7	1
Aortic regurgitation (0–3)	0.9 ± 0.7	0.92 ± 0.7	.85
Mean transaortic gradient (mmHg)	42 ± 15	46 ± 15	.09
Ejection fraction (%)	55 ± 12	55 ± 13	1
E/e' septal	22 ± 10	18 ± 7	.005
Tricuspid regurgitation Vmax	2.6 ± 0.4	2.9 ± 0.5	.0001
TAPSE baseline (mm)	19.7 ± 5	20.3 ± 5	.44
LBBB before TAVI	13 (19%)	16 (16%)	.61
Pacemaker present	6 (9%)	9 (9%)	.44
Log BNP	2.4 ± 0.5	2.3 ± 0.6	.24

LVEDP: left ventricular end-diastolic pressure.

Data are presented as mean ± SD. Significant p values (<.05) are highlighted in bold.

pacemaker (not present at baseline) was indicated in 46 patients (27%).

Right ventricular function parameters in the whole group did not change significantly (baseline TAPSE = 20.03 ± 5.4 mm; six months after TAVI the average TAPSE = 20.12 ± 5.2 mm; $p = .73$).

Parameter variation as determinants of a change in PAP 6 months after TAVI

In univariate and multivariate analyses, only the change in E/e' ratio was a predictor of a change in PAP (Table 5, Figure 3).

Discussion

The main findings of this study in patients with severe AS treated with TAVI were: (1) the independent determinants of the baseline value of the PAP were BMI, the GOLD classification of COPD, aortic regurgitation and E/e' ratio, (2) there was a significant improvement in PAP 6 months after TAVI, with significantly less patients having PHT, (3) the baseline parameters predicting an improvement in PAP were the tricuspid regurgitation velocity and the E/e' ratio, and (4) the change in E/e' ratio was the only predictor of a change in PAP.

PHT is noted in 28–56% of the patients with AS, depending on the definition threshold [3,4,7,9] and clinical characteristics. Elderly persons with severe AS undergoing TAVI may have several comorbidities, especially COPD, leading to a significant increase in PAP that is relatively unrelated to AS. They may also have concomitant regurgitant lesions of the left heart valves that contribute to an increase in PAP. In our study, PHT was present in 51% of patients. Several factors were shown to be related to a rise in PAP in univariate analysis: the GOLD classification of COPD,

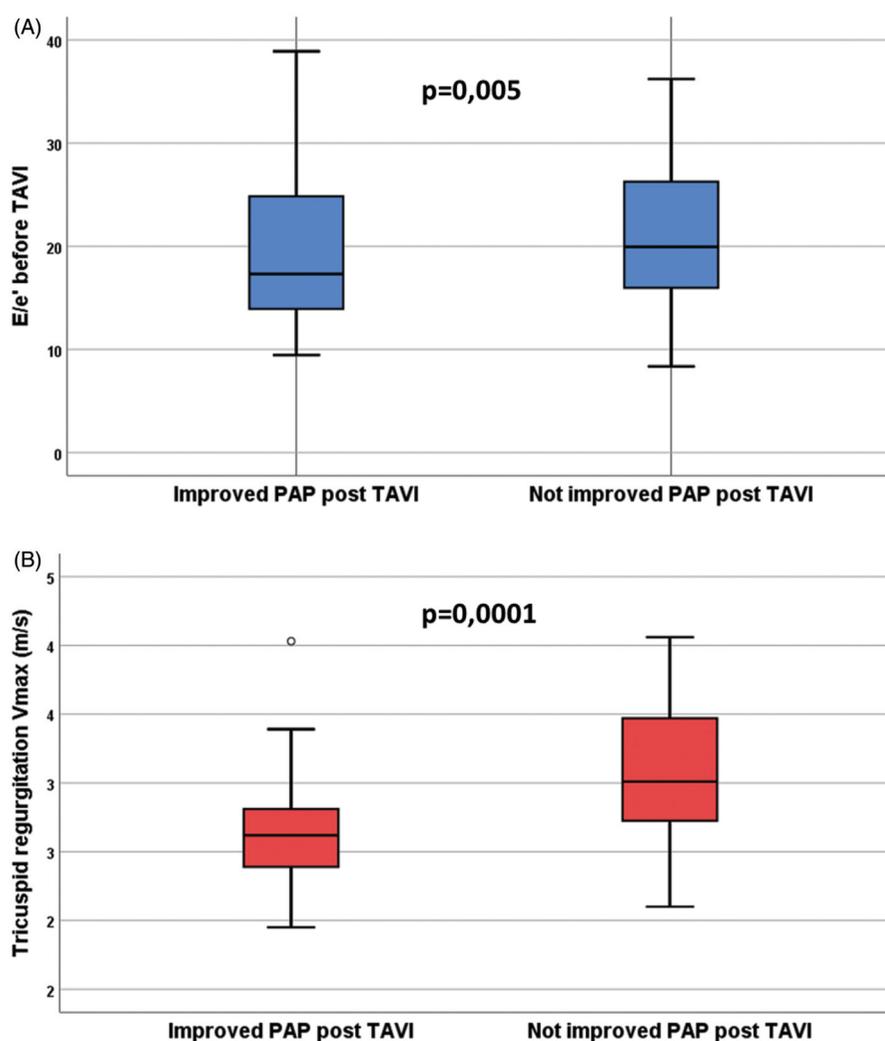


Figure 2. Comparison between the groups of patients who improved their transtricuspid gradient 6 months after TAVI implantation (left boxplots) and the ones who did not improve or increased their gradient (right boxplots). The only significantly different parameters measured at baseline (before TAVI) according to our analysis were the E/e' ratio (A) and maximal velocity of the tricuspid regurgitation (B). The higher E/e' ratio and higher transtricuspid gradient probably reflect a more advanced state of disease in the patients who did not show improvement in pulmonary artery pressure after TAVI.

Table 4. Variation of clinical and echocardiographic variables after TAVI.

Variable	Mean variation \pm SD	95% confidence interval		<i>p</i>
		Lower	Upper	
NYHA class (I–IV)	-0.9 ± 0.8	-1.05	-0.81	<.0001
Tricuspid regurgitation peak velocity	-0.1 ± 0.4	-0.04	-0.16	.001
Mean transaortic gradient (mmHg)	-35 ± 16	-38	-33	<.0001
Mitral regurgitation (0–3)	-0.05 ± 0.6	-0.14	0.05	.326
Aortic regurgitation (0–3)	-0.09 ± 0.9	-0.24	0.05	.198
Ejection fraction (%)	-0.03 ± 9	-1.38	1.32	.966
E wave amplitude (cm/s)	5 ± 26	1.2	9.21	.01
A wave amplitude (cm/s)	13 ± 27	8.32	18.03	<.0001
E/A ratio	-0.09 ± 0.55	-0.19	0.003	.058
E wave deceleration time (ms)	12 ± 99	-4	28	.147
Septal e' (cm/s)	0.24 ± 1.6	-0.01	0.50	.065
E/e' ratio	-0.18 ± 7.3	-1.03	1.38	.770
TAPSE (mm)	-0.09 ± 3	-0.59	0.42	.733
Log ₁₀ NT-proBNP	0.13 ± 0.5	0.05	0.20	.002

Data are presented as mean \pm SD. Significant *p* values (<.05) are highlighted in bold.

mitral or aortic regurgitation, E/e' ratio, and ejection fraction. Surprisingly, the trans-aortic gradient did not

reach statistical significance. Moreover, the multivariable model including these parameters yielded only

Table 5. Parameter variation as determinants of pulmonary artery pressure change 6 months after TAVI.

Δ parameter	Mean variation \pm SD	Univariate analysis		Multivariable analysis	
		Beta	<i>p</i>	Beta	<i>p</i>
Δ mean transaortic gradient (mmHg)	-35 ± 16	-0.11	.16	-0.07	.45
PCI with TAVI		0.09	.25	0.02	.86
Δ mitral regurgitation (0–3)	-0.10 ± 0.58	0.09	.22	-0.11	.21
Δ aortic regurgitation (0–3)	-0.12 ± 0.94	0.12	.13	0.17	.07
Δ ejection fraction (%)	0.09 ± 8.55	-0.13	.11	-0.01	.96
Δ <i>E/e'</i> ratio	-0.04 ± 7.36	0.27	.001	0.23	.01
Δ TAPSE (mm)	-0.1 ± 3	0.09	.19	0.01	.84
New onset LBBB after TAVI		0.06	.44	0.06	.55
New pacemaker implantation		0.09	.24	0.12	.21

CI: confidence intervals; PCI: percutaneous coronary intervention; SD: standard deviation. Data are presented as mean \pm SD. Significant *p* values ($<.05$) are highlighted in bold.

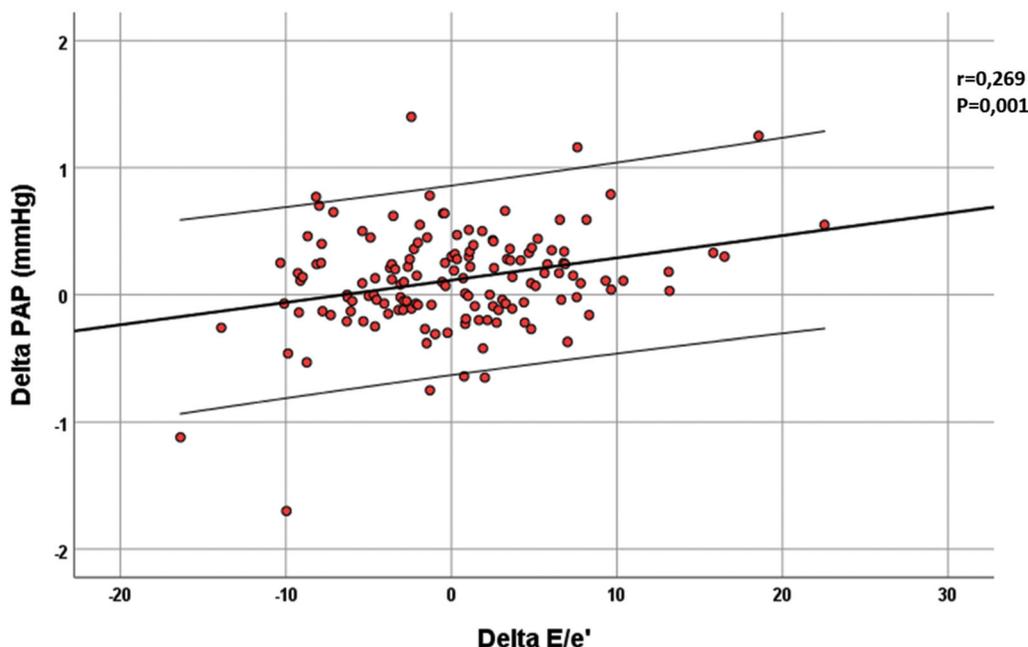


Figure 3. Correlation plot between the variation of the *E/e'* ratio before and after the TAVI procedure (delta *E/e'*) and the variation of the pulmonary artery pressure (delta PAP) as derived from the maximal transtricuspid gradient. A correlation line was fitted to the data (central thick line), as well as 95% confidence intervals (thin lateral lines).

four independent predictors for PHT: COPD severity, filling pressures of the left ventricle, reflected by the *E/e'* ratio, BMI and aortic insufficiency. This is in concordance with data already present in the literature, showing that diastolic function of the left ventricle is the main predictor of elevated PAP in severe AS [12]. The role of COPD severity is obvious, especially in this elderly population in whom chronic pulmonary disease is not rare. The fact that BMI was not significant in the univariate analysis, but very significant in the multivariate cannot be explained by our statistical model, but the result is consistent with previous findings [19]. It could be due to the influence of the BMI on the prevalence of hypertension, diabetes and coronary artery disease (factors that were not entered in the multivariable analysis due to their lack of impact in the univariate model). Numerous publications address the prognostic role of the postprocedural

paravalvular leak [20], but there is very little recent data on the impact of pre-procedural native valve aortic insufficiency associated to AS [21].

In our study, there was an overall statistically significant improvement in PAP, but only 59% really improved, and only 21% normalised the PAP. The value of the PAP was unchanged or even worsened in 41%. This may explain the little overall variation of the mean PAP. There was also a significant improvement in transaortic gradient without significant changes in the ejection fraction and the overall degree of mitral and aortic insufficiency. The effect of TAVI on the ejection fraction has indeed been reported as either neutral or positive [22–24]. In a recent meta-analysis, a non-significant trend towards a reduction in mitral regurgitation was reported [25], consistent with our findings. The change in aortic regurgitation is of course, very variable, depending on the baseline

characteristics of each patient as well as numerous technical factors [26].

It has already been noted that PAP improves after successful TAVI intervention (according to VARC 2 criteria [20]). This is most likely due to the removal of the valvular obstacle and the possible improvement in left ventricular systolic and diastolic function or valvular regurgitation. The persistence of PHT is considered to impact long-term prognosis in patients with severe AS [11]. The improvement in PAP was related to the initial value of the PAP and the E/e' ratio. Very few studies investigated this particular matter, and only in the setting of surgical valvular replacement, but the results are similar [5,27]. Higher values of PAP and E/e' may suggest a more advanced disease in which the beneficial effects after TAVI may be less important. The only independent dynamic variable predicting a change in PAP after TAVI proved to be the change in the E/e' ratio.

The general clinical improvement, demonstrated by a significant decrease of the NYHA class, was reflected in echocardiography by a decrease in tricuspid regurgitation peak velocity and mean transaortic gradient (Table 4). This improvement was correlated with a similar evolution of the biomarkers of elevated intracardiac pressure, as observed in heart failure in general [28] and in elderly patients with AS [13].

After TAVI, the mitral inflow E and A waves had significantly higher amplitudes, but the E/e' ratio did not change considerably. The E/e' ratio has a paradoxical evolution: although it was a significant determinant of the baseline PAP and of the improvement in PAP, its mean value did not change significantly. There could be several explanations to the paradoxical behaviour of this parameter, that does not change in spite of the significant change in PAP. One explanation may reside in an early and sustained increase in cardiac output after relieving the aortic obstacle (as reflected by the rise in E and A velocities through an unchanged mitral valve). Also, improvement of the septal e' velocity could be limited in the presence of a prosthetic valve very close to the mitral septal point. However, the role of the diastolic function as measured by the E/e' ratio is reinforced by the fact that the other main potential factors influencing the PAP (left heart valvular regurgitation, LV ejection fraction, severity of the pulmonary disease and right ventricular function) did not show any significant correlations in this study.

The debate on the optimal site of e' measurement is still going on but the septal site seems to correlate best to direct and indirect measurements of LV filling pressures [13,29,30].

A new-onset LBBB or the implantation of a new pacemaker did not demonstrate a significant effect on the PAP in our patients, in univariate and multivariate analysis.

Clinical implications

PAP evaluation by echocardiography needs to be a part of the prognostic estimation of potential TAVI candidates [20, 31], along with the filling pressures of the left ventricle, the two elements being interconnected. COPD and obesity remain clinical features to be considered when estimating the role of AS in the rise of PAP. The improvement in the filling pressures of the left ventricle after relieving the valvular obstacle, although insignificant on the population level, seems to be the main factor contributing to the reduction in PAP.

Study limitations

This is a retrospective cross-sectional study, but the quality of the data was not compromised because data acquisition has been done according to a very strict prospectively defined TAVI protocol. The limited number of patients is also a potential problem in interpreting statistical models, especially when the number of variables is important. However, the level of statistical significance was sufficient to sustain our conclusions. The evaluation of PAP by echocardiography has several known limitations [32,33] but was preferred due to its lack of risk for the patient, as compared to invasive measurements. Finally, in AS patients, the evaluation of the aortic regurgitation is already difficult [17]. Estimating its change can be even more so, since it is a comparison of valvular regurgitation with a paraprothetic leak.

Conclusions

Independent predictors for baseline PAP in elderly patients with symptomatic AS were the BMI, GOLD class and left ventricular filling pressure reflected by the E/e' ratio. The baseline variables related to a change in PAP 6 months after TAVI were the baseline PAP and E/e' , with only the change in the E/e' ratio being correlated to the change in PAP.

Disclosure statement

No potential conflict of interest was reported by the authors.

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