Incidence, Predictors, and Impact on Prognosis of Systolic Pulmonary Artery Pressure and its Improvement After Transcatheter Aortic Valve Implantation: A Multicenter Registry

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ABSTRACT: Aims. Elevated values of systolic pulmonary artery pressure (sPAP) represent a common finding in patients with aortic stenosis and severe left ventricular hypertrophy. Prognostic impact of sPAP and its potential improvement after transcatheter aortic valve implantation (TAVI) remains to be determined. **Methods and Results.** This is a multicenter retrospective registry in five European institutions. All consecutive patients undergoing TAVI were enrolled, and divided into two groups according to sPAP evaluated with echocardiography: ≤40 mm Hg and >40 mm Hg. All-cause mortality at follow-up of at least 1 year was the primary endpoint, while 30-day mortality, periprocedural complications, myocardial infarction, stroke, and reintervention rates at follow-up were the secondary endpoints. Among 674 patients enrolled, a total of 319 (47%) had sPAP >40 mm Hg. This was associated with higher mortality at 30 days (4.5% vs 8.5%; *P*=.03) and at a median follow-up of 477 days (17% vs 26%; *P*=.03). Improvement of sPAP was reported in 113 patients (27%), occurring more frequently in absence of moderate or severe mitral regurgitation and of right ventricle dysfunction. With multivariate adjustment, reduced renal function, insulin-dependent diabetes mellitus, and sPAP >40 mm Hg were independent predictors of all-cause mortality, improvement in sPAP values was related to a better survival, while ejection fraction was not. **Conclusion.** Elevated values of sPAP represent a common finding in patients undergoing TAVI. This parameter, along with its improvement, may be used to stratify risk and determine prognosis for patients undergoing TAVI.

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Elevated values of systolic pulmonary arterial pressure (sPAP) represent a common finding (up to 25%) in patients with severe aortic stenosis (AS), due to the increased filling pressures in hypertrophied left ventricles, which are transmitted to pulmonary vessels.[1-3] Moreover, the persistency of elevated values of pulmonary pressure may result in the development of reactive hypertrophy in the arteriolar tree, leading to an increase of pulmonary resistances and to a clinical worsening.[4]

Presence of increased sPAP enhances the risk of death and recurrence of heart failure[5,6] in patients medically treated, while it was demonstrated to predict perioperative complications and in-hospital and long-term outcomes[7,8] for those undergoing surgical aortic valve replacement (AVR), thus justifying its evaluation in risk scores, such as the EuroSCORE.[9,10]

Previous experiences[11-15] reported an increased risk of death at long-term follow-up in patients with elevated sPAP values undergoing TAVI, while the work of Ben-Dor et al[1] demonstrated the reduction of pulmonary pressure values after TAVI.

However, sPAP probably does not represent a unique disease in patients with severe AS, being potentially reversible or not, according to progression and severity of AS and to other structural changes of both the heart and the pulmonary vessels. Thus, we have performed a multicenter study to appraise independent predictive value of pulmonary artery hypertension (PAH), frequency, and clinical significance of its improvement after TAVI.

Methods

Study design, setting, and participants. The present study is a multicenter, retrospective registry that is reported in accordance with the STROBE statement.[16]

Consecutive patients with severe symptomatic AS referred for TAVI at five European Institutions (Torino, Catania, Milano, and Padova in Italy, and Utrecht in the Netherlands) from January 2007 to December 2012 were included.

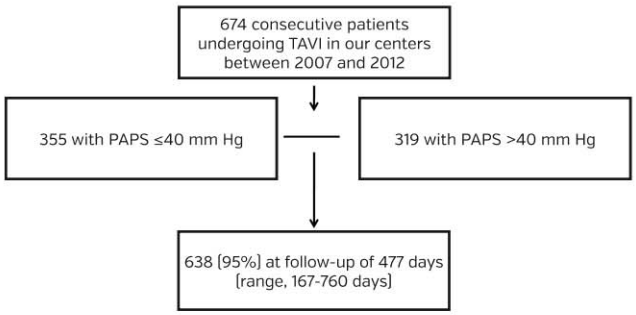

FIGURE 1. Included patients and follow-up.

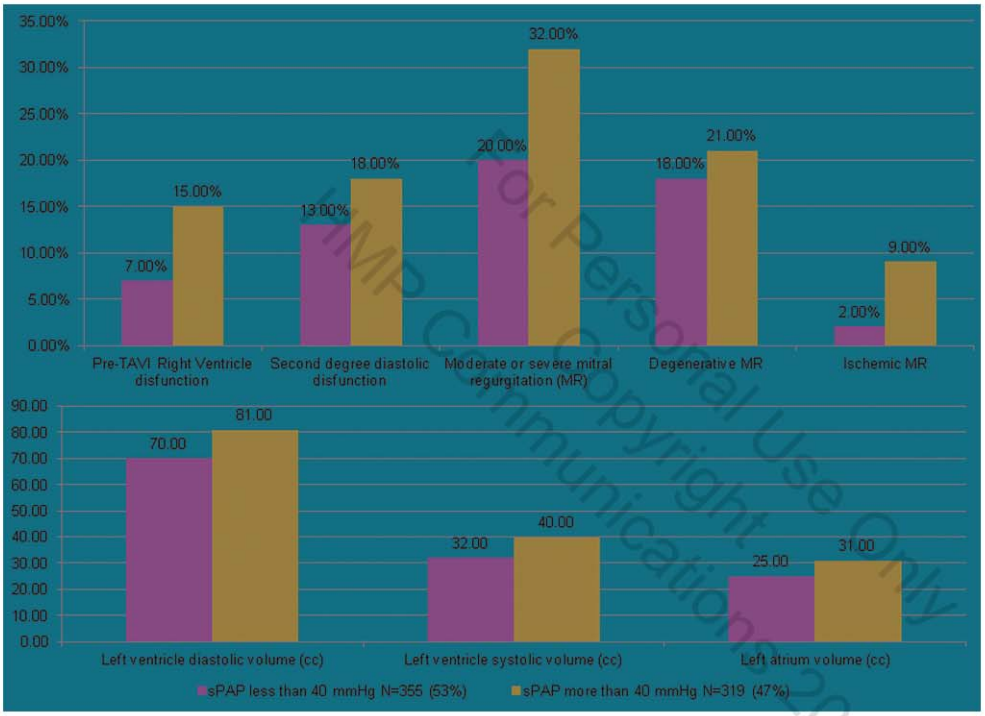

FIGURE 2. Echocardiographic data (all $P<.05$).

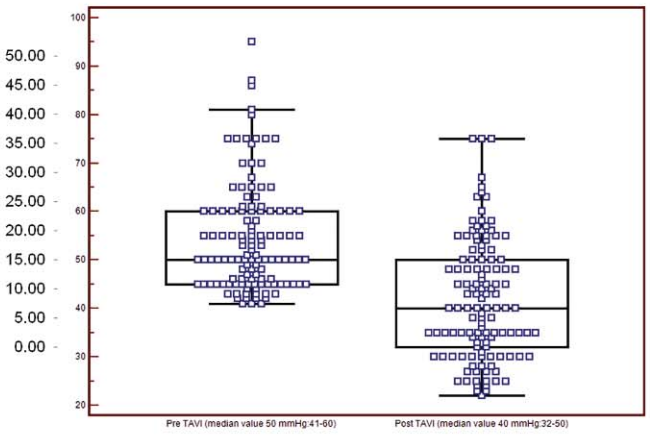

FIGURE 3. Reduction in sPAP for patients with baseline value >40 mm Hg.

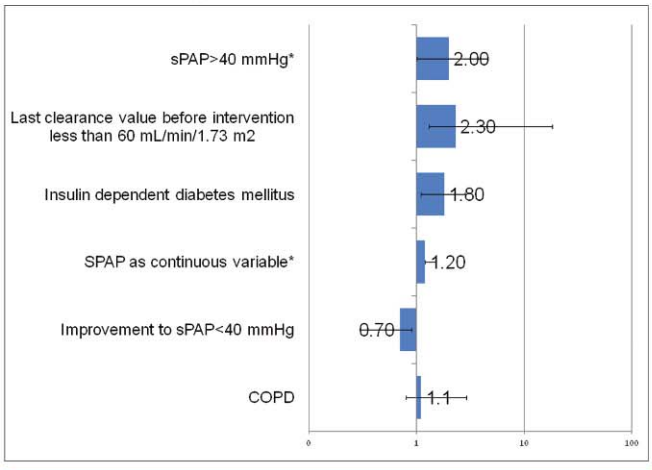

FIGURE 4. Independent predictors of all-cause death at mid-term follow-up.

In each center, indication for TAVI was appraised after consensus by a team of cardiac surgeons, cardiologists, and anesthetists. Patients with pulmonary arterial hypertension were denied TAVI after Heart Team evaluation due to negative life expectancy. Coronary anatomy and hemodynamic status were assessed by coronary angiography and left heart catheterization. Valvular anatomy and annulus size were evaluated with transthoracic and transesophageal echocardiography, contrast angiography of the aortic root, and multislice computer tomography of the thoracic aorta. The vascular access site was assessed by color Doppler sonography and multislice computer tomography with contrast angiography of the aorto-ilio-femoral system. Transfemoral, transsubclavian, direct aortic, and transapical approaches were performed according to the expertise of each center, with implantation of Medtronic CoreValve or Edwards Sapien/Sapien XT prosthesis.

Clinical variables and endpoints. Systolic pulmonary arterial pressure was calculated by adding transtricuspid pressure gradient to mean right atrial pressure estimated from inferior vena cava diameter and motion during respiration as follows: mean right atrial pressure was estimated to be 5 mm Hg if there was complete collapse of a normal inferior vena cava during inspiration; 10 mm Hg if a normal inferior vena cava collapse was >50%;

Table 1. Baseline features.

	sPAP ≤40 mm Hg N = 355 (53%)	sPAP >40 mm Hg N = 319 (47%)	*P*-Value
Age (years)	81.38 ± 5.6	81.58 ± 5.6	.69
Female gender	103 (47%)	127 (54%)	.55
Non-insulin dependent diabetes	103 (29%)	83 (26%)	.95
Insulin-dependent diabetes	39 (17%)	28 (14%)	.95
Previous myocardial infarction	71 (20%)	68 (21%)	.48
Previous percutaneous coronary intervention	120 (34%)	103 (32%)	.35
Previous coronary artery bypass graft	56 (16%)	35 (11%)	.86
Carotid artery disease[a]	57 (31%)	48 (31%)	.57
Peripheral artery disease[a]	40 (15%)	53 (16%)	.06
Previous stroke	35 (10%)	42 (13%)	.11
Chronic obstructive pulmonary disease[b]	111 (32%)	107 (34%)	.43
NYHA class	2.68 ± 0.65	2.88 ± 0.63	.05
Last clearance value before intervention (GFR) (mL/min/1.73 m²)[c]	52.5 ± 23	48.8 ± 24.4	.06
Logistic EuroSCORE[d]	17.18 ± 13.10	18.46 ± 18.90	.41
STS score mortality[e]	9.4 ± 8.4	8.7 ± 6.7	.31
ACEF[f]	1.8 ± 0.6	2.2 ± 0.8	.14

[a]According to the Society of Thoracic Surgeons definition. [b]Evaluated according to Global Strategy for the Diagnosis, Management and Prevention of COPD: 2003 update. [c]Cockcroft-Gault Calculator (http://nephron.com/cgi-bin/CGSIdefault.cgi). [d]http://www.euroscore.org/calc.html. [e]http://209.220.160.181/STS-WebRiskCalc261/

15 mm Hg if a dilated inferior vena cava collapsed by >50% with inspiration; and 20 mm Hg if there was no visible evidence of dilated inferior vena cava collapse.[17]

Ejection fraction, mitral regurgitation, aortic regurgitation, and right ventricle dysfunction were appraised and evaluated through different parameters according to current guidelines.[18-20]

Patients were divided into two groups; those with sPAP ≤40 mm Hg, and those with sPAP >40 mm Hg as suggested by recent guidelines.[21] The value of PAH at the last echocardiogram before TAVI was considered for this study. Moreover, patients were divided according to change of sPAP after TAVI; those with an improvement (a shift from values above to below 40 mm Hg) and those without. All values of sPAP were appraised at their last follow-up contact after discharge.

The primary endpoint was the rate of all-cause mortality as defined by the Valve Academic Research Consortium (VARC) at mid-term follow-up.[17] Secondary endpoints were appraised both at 30 days (all-cause mortality, periprocedural and spontaneous myocardial infarction, transient ischemic attack, stroke, bleedings, major vascular complications) and at mid-term follow-up (myocardial infarction, transient ischemic attack, stroke, prosthesis dysfunction). All outcomes were adjudicated according to VARC statement.[13]

In order to assess all procedural and in-hospital outcomes, institutional electronic database and individual patient charts were consulted.

Short-term and mid-term outcomes with at least 6-month follow-up were recorded by phone, formal query to primary physicians, and outpatient visits.

Statistical analysis. Continuous variables are expressed as mean ± standard deviation and were compared with ANOVA. Categorical variables are presented as counts and percentages and were compared with the chi-squared test. To adjust for difference in length of follow-up, Cox multivariate analysis was exploited for efficacy endpoint and mid-term death including all variables with significant differences ($P<.05$) at baseline for patients with and without elevated values of sPAP.[18,19] Sensitivity analysis was performed after excluding patients with a diagnosis of chronic obstructive pulmonary disease. Moreover, independent predictors of improvement of sPAP were searched for through logistic regression, exploiting all variables with a significant difference ($P<.05$) at baseline. To assess validity of the Cox proportional hazard model, proportional assumptions hazard was checked graphically. To assess validity of the logistic regression model, a Hosmer Leemshow test was performed. Statistical significance was set at the two-tailed .05 level. Computations were performed with SPSS 21.0 (SPSS).

Results

From a total of 674 patients included, a total of 355 (53%) had sPAP ≤40 mm Hg, while 319 (47%) had sPAP >40 mm Hg (Figure 1). In the first group, the median sPAP was 35 mm Hg (interquartile range [IQR], 30-38 mm Hg), while in the second it was 50 mm Hg (IQR, 41-60 mm Hg).

As reported in Table 1, the two groups did not show significant differences in baseline features, with a trend toward a worse New York Heart Association class and increased surgical risk scores for patients with higher sPAP values.

Patients with sPAP >40 mm Hg (Table 2) showed a lower ejection fraction before TAVI (51.4 ± 13.8 vs 55.6 ± 5.9; $P<.001$) and after TAVI (51.0 ± 11.6 vs 56.0 ± 12.0; $P=.04$), while no differences in the choice of approach and kind of valve were reported. Patients with elevated sPAP values had larger left ventricle volumes and higher rates of diastolic dysfunction, moderate to severe mitral regurgitation, and right ventricle dysfunction (Figure 2).

At 30 days (Table 3), patients with sPAP >40 mm Hg died more frequently (both all-cause [4.5% vs 8.5%; $P=.03$]

Table 2. Echocardiographic assessment and procedural features.

	sPAP ≤40 mm Hg n = 355 (53%)	sPAP >40 mm Hg n = 319 (47%)	*P*
Pulmonary pressure (mm Hg)	31.69 ± 5.6	46.07 ± 5.07	<.001
Ejection fraction (%)	55.60 ± 5.86	51.4 ± 13.8	<.001
Ejection fraction <30%	4 (1%)	20 (6.3%)	<.001
Aortic valve area (cm²)	0.60 ± 0.19	0.64 ± 0.189	.20
Mean aortic gradient (mm Hg)	49.6 ± 15	48.9 ± 16.1	.11
Aortic valve insufficiency (mild, moderate, and severe)	72 (31%)	93 (43%)	.01
Severe and moderate mitral valve insufficiency	87 (28%)	74 (29%)	.63
Approach			
Transfemoral	255 (72%)	227 (71%)	.07
Transapical	67 (19%)	47 (15%)	
Transsubclavian	32 (9%)	44 (13%)	
Prosthesis diameter			.06
23 mm	53 (23%)	19 (41%)	
26 mm	128 (55%)	106 (49%)	
29 mm	51 (22%)	63 (29%)	
31 mm	0 (0%)	4 (2%)	
Kind of device			.06
CoreValve	99 (43%)	116 (53%)	
Edwards	134 (56%)	102 (46%)	
Ejection fraction	56 ± 12	51.0 ± 11.6	.04
Mean aortic gradient (mm Hg)	10.6 ± 5.9	10.9 ± 5.1	.53
Aortic valve insufficiency (mild, moderate)	22 (6.2%)	15 (4.7%)	.24
Pulmonary pressure values	31.12 ± 9.5	41.37 ± 11	<.001

Table 3. Thirty-day events.

	sPAP ≤40 mm Hg n = 355 (53%)	sPAP >40 mm Hg n = 319 (47%)	*P*
Death for any cause*	16 (4.5%)	27 (8.5%)	.03
Cardiovascular death*	14 (4.5%)	23 (8%)	.03
Transient ischemic attack*	5 (1.6%)	2 (0.8%)	.32
Stroke*	3 (0.9%)	7 (2.6%)	.11
Bleeding*			.06
Life threatening	28 (8%)	43 (17%)	
Major bleeding	66 (19%)	37 (12%)	
Minor bleeding	35 (10%)	28 (9%)	
Major vascular complications*	27 (8.6%)	24 (8.6%)	.56
Minor vascular complications*	48 (14%)	44 (15%)	.45

*VARC definitions.

and cardiovascular [4.5% vs 8%; *P*=.03]), in the absence of a significant increase of perioperative complications.

Similarly, at a median follow-up of 477 days (IQR, 167-760 days), patients with increased pulmonary arterial pressure showed higher mortality, both all-cause (17% vs 33%; *P*=.03) and cardiovascular (15% vs 31%; *P*=.01) (Table 4).

In the entire cohort of patients with high sPAP, there was a reduction of sPAP from median values of 50 mm Hg (IQR, 41-60) to 40 mm Hg (IQR, 32-50 mm Hg). In detail, improvement of sPAP from above to below 40 mm Hg was reported in 113 patients (27%). Systolic pulmonary artery pressure reduction was more frequent in the absence of moderate or severe mitral regurgitation and absence of right ventricle dysfunction (odds ratio [OR], 2; 95% confidence interval [CI], 1.3-4 and OR 4.20; 95% CI, 2-16) (Figure 3).

At multivariate adjustment, insulin-dependent diabetes mellitus, reduced renal function, and sPAP (both as continuous variable and as more than 40 mm Hg) were independent predictors of all-cause death (Figure 4).

Moreover, independent of ejection fraction and diagnosis of chronic obstructive pulmonary disease, sPAP improvement appears to reduce risk of adverse events (hazard ratio [HR], 0.7; 95% CI, 0.5-0.9; *P*=.04) (Table 5, Figure 4).

Significance of the results did not change at sensitivity analysis, after excluding patients with a diagnosis of COPD (Tables 5 and 6).

Discussion

The main findings of this multicenter registry are: (1) elevated values of sPAP are frequent in patients with severe aortic stenosis undergoing TAVI and negatively affect prognosis; (2) patients with high sPAP and concomitant moderate to severe mitral regurgitation and/or right ventricular dysfunction show less likelihood of sPAP improvement; and (3) recovery of normal sPAP values significantly improves prognosis.

High sPAP values represent a common finding for patients with severe aortic stenosis with a negative effect on prognosis. Elevated ventricular pressure values due to hypertrophied heart trough enhance systolic pressure in the pulmonary vessels via "backward transmission."[1] From a clinical point of view, as reported in other studies,[10-15] this acts as a negative long-term prognostic factor, probably due to severe dysfunction of both heart ventricles and to the presence of co-pathologies like mitral regurgitation.

Table 4. Long-term follow-up events.

	sPAP ≤40 mm Hg n = 355 (53%)	sPAP >40 mm Hg n = 319 (47%)	*P*
Death for any cause*	58 (17%)	78 (26%)	.03
Cardiovascular death*	25 (15%)	40 (31%)	.01
Myocardial infarction	15 (5%)	5 (2%)	.06
Transient ischemic attack*	5 (1.6%)	4 (1.6%)	.62
Stroke*	27 (9%)	28 (8%)	.58
Need for reintervention	2 (0.7%)	–	.32

*VARC definitions.

Table 5. Long-term follow-up events after excluding patients with a diagnosis of chronic obstructive pulmonary disease.

	sPAP ≤40 mm Hg n = 230 (54%)	sPAP >40 mm Hg n = 199 (46%)	*P*
Death for any cause*	38 (17%)	52 (28%)	.03
Cardiovascular death*	13 (6%)	28 (14%)	.01
Myocardial infarction	10 (4%)	4 (2%)	.04
Transient ischemic attack*	2 (1%)	2 (1%)	.57
Stroke*	23 (5%)	23 (4%)	.61
Need for reintervention	2 (0.7%)	–	.32

*VARC definitions.

Table 6. Cox multivariate adjustment for long-term all-cause death.

	HR	LCI	UCI	*P*
Age	0.98	0.93	1.1	.60
Insulin-dependent diabetes mellitus	1.3	0.9	3.2	.09
Ejection fraction <30%	1.4	0.6	4.4	.76
Last clearance value before intervention less than 60 mL/min/1.73 m²	4.3	1.3	12	.01
sPAP >40 mm Hg*	2.1	1.4	5.1	.02
SPAP as continuous variable*	1.3	0.76	1.5	.12
Improvement to sPAP <40 mm Hg	0.4	0.3	0.9	.049

*The same model was performed twice for these two variables.

Patients with elevated values of sPAP being evaluated by the Heart Team for TAVI should not be viewed as a uniform population. As described by Dor et al,[1] and in our study as well, the recovery of normal values of pulmonary pressure after TAVI represents a common finding, with results confirmed at more than 1 year of follow-up. More than one-third of patients showed a failure to restore normal sPAP values after TAVI, probably because pulmonary pressure was "out of proportion" to that expected from the increase of left heart pressure; this also could be related to an increase in pulmonary artery vasomotor tone or to pulmonary vascular changes. For these patients, secondary PAH may reflect "remodeling" of the pulmonary arterial wall with abnormalities of elastic fibers, intimal fibrosis, and medial hypertrophy that result in vascular stiffness and reduced vasodilator responsiveness. In the present study, moderate or severe mitral regurgitation and right ventricle dysfunction were closely related to absence of recovery of normal values, independently from ejection fraction. Actually, both these clinical conditions cause a longer and more severe exposition to enhanced pressures, leading to absence of reversibility even if severe aortic stenosis has been efficaciously treated. Moreover, the absence of clinical significance of chronic obstructive pulmonary disease in this cohort, despite its presence in a significant number of patients, may stress the prevalent relationship between cardiac disease and pulmonary arterial pressure.

Recovery to normal pulmonary pressure value was independently related to a better prognosis. The reduction of sPAP values below 40 mm Hg may depict a population without the "out of proportion" phenomenon,[23] thus without structural and hormonal changes due to a longer exposition to elevated left heart pressures. These data also reflect the experience of balloon aortic valvuloplasty, that is a benefit derived from larger valve area after interventions, probably with a reduced intraventricular pressure and consequent impact on pulmonary vessels.[24] From a clinical point of view, these data may help to select patients for TAVI. Those with sPAP values >40 mm Hg with moderate to severe mitral regurgitation or with right ventricular disease would probably not benefit from a reduced "stress" on an already deeply modified pulmonary vessel tree, with a consequent small or neutral effect on prognosis. This hypothesis may be confirmed by the results of exclusion of patients with a diagnosis of COPD, which showed similar results in terms of survival.

Apart from sPAP, renal failure and diabetes mellitus were other predictors of poor outcome. It has already been shown that renal impairment has a negative impact on prognosis,[21] because it leads to a high risk of bleeding. Moreover, the additional risk of insulin-treated diabetes mellitus may be related to the numerous diabetes-related complications that this patient category experiences.[26,27]

Study limitations. Our work shares many limitations of observational non-randomized evidence, although it was multicenter, thus limiting potential bias. A major limitation is that the measurement of PAP is estimated with echocardiography, which, although inexpensive, non-invasive, risk-free, and widely exploited, performs less accurately than invasive right heart catheterization. Moreover, multivariate analysis, as explained in

the literature, may be viewed as a potential explanation of clinical phenomena,[22] although without the accuracy of randomized evidence. In the present case, the graphical demonstration of hazard assumption demonstrated an increase of the risk as the covariates were added. Finally, the Hosmer Leemshow test was not significant, stressing the accuracy of logistic regression.

Conclusion

Elevated values of sPAP represent a common finding in patients undergoing TAVI. This parameter, along with its improvement, may be used to stratify risk and determine prognosis for patients undergoing TAVI.

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