Clinical Impact and Prognosis of Pulmonary Hypertension after Transcatheter Aortic Valve Implantation

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Abstract

Background: Transcatheter Aortic Valve Implantation (TAVI) is a therapeutic option for patients presenting with severe aortic stenosis and in whom surgery is contraindicated. Pre-procedural Pulmonary Hypertension (PH) has been shown to be a factor of poor prognosis in surgical and TAVI studies.

Aims: We sought to evaluate the clinical impact and prognostic implications of the presence of post-TAVI PH.

Methods: The outcome of post-TAVI Pulmonary Artery Systolic Pressure (PASP) was studied in 58 high-risk patients with severe symptomatic aortic stenosis, by assessing clinical presentation and prognosis and determining predictive factors.

Results: Post-TAVI PH (PASP>40 mmHg) affected 43% of patients at 6 months. Despite excellent aortic results in both groups, patients with post-TAVI PH were more symptomatic, with a higher NYHA classification and a more frequent readmission for cardiac failure. On univariate analysis, factors for elevated PASP were: female sex, history of myocardial infarction, mitral regurgitation, and degree of mitral regurgitation. On multivariate analysis, only elevated PASP remained an independent factor for post-TAVI PH.

Conclusion: PH is frequently present after TAVI and allows identification of a subgroup of patients with poorer clinical presentation and cardiovascular prognosis. Further studies and especially complementary myocardial investigation seem necessary.

Keywords: Aortic stenosis; Transcatheter aortic valve implantation; Pulmonary hypertension

Abbreviations: TAVI: Transcatheter Aortic Valve Implantation; PH: Pulmonary Hypertension; PASP: Pulmonary Artery Systolic Pressure; NYHA: New York Heart Association; BNP: Brain Natriuretic Peptide; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; STS Score: Society of Thoracic Surgeons Score; VARC 2: Valve Academic Research Consortium; MR: Mitral Regurgitation; AR: Aortic Regurgitation; ACE: Angiotensin-Converting-Enzyme

Introduction

Aortic stenosis is the most frequent valvular disease in the elderly population [1]. Since 2002, TAVI (Transcatheter Aortic Valve Implantation) has emerged as a therapeutic option for patients presenting with severe aortic stenosis and is contraindicated [2-4]. Pulmonary Hypertension (PH) is frequently present in aortic stenosis3 and its reduction has been shown after TAVI [4,5]. Its presence is known to be a factor of poor prognosis in aortic stenosis. Pre- and post-operative PH has been shown to be associated with reduced post-surgical survival[6], and pre-procedural PH to be associated with higher post-TAVI mortality [5].

We sought to evaluate clinical impact and prognosis of post-procedural PH by identifying a subgroup of patients with high pulmonary pressure after TAVI and searching for its predictive factors. To our knowledge, this is the first study to measure the outcome of pulmonary pressures months after TAVI [6].

Methods

Study population

This study analyzes prospectively all patients undergoing TAVI with a CoreValveTM device (Medtronic CV, Irvine, CA) in our center between November 2008 and December 2010. All presented with criteria for severe aortic stenosis as defined in the most recent recommendations and were symptomatic [7]. TAVI was indicated after evaluation of each medical situation by a multidisciplinary staff, after contraindicating surgical aortic valve replacement because of excessive perioperative risk. All patients gave written informed consent.

Study design

Baseline assessment: Initial assessment involved evaluation of clinical symptoms and NYHA (New York Heart Association) score,
EuroSCORE and STS score were calculated in order to estimate perioperative risk. Brain Natriuretic Protein levels (BNP, normal<100 pg/mL) were measured. Echocardiography was performed, with measurement of the usual aortic severity assessment parameters (indexed aortic valve area, mean aortic gradient, velocity ratio). Left Ventricle Ejection Fraction (LVEF), and grading of any other valvulopathy, LV diastolic function was assessed by measuring left atrial area. Doppler mitral flow velocity (E/A) and the ratio of mitral early diastolic flow velocity to tissue Doppler mitral annular lengthening velocity (E/E'). Pulmonary Artery Systolic Pressure (PASP) was calculated by adding tricuspid gradient to mean right atrial pressure. Trans tricuspid gradient was obtained from the maximum tricuspid regurgitation jet velocity in continuous-wave Doppler, and considered as equal to right ventricular systolic pressure in the absence of right ventricular obstruction [8,9]. Right atrial pressure was determined from the diameter of the inferior vena cava and its motion during respiration [5]. Echocardiographic evaluation of PASP is known to correlate strongly with catheterization measurement [10].

Pulmonary hypertension was defined as PASP >40 mmHg, normal PASP being estimated at 33 mmHg in a population of 90 year-olds [11].

**TAVI procedures:** The Corevalve TM self-expandable device (Medtronic CV, Irvine, CA), used in all patients, consists of a trileaflet porcine pericardial valve inside a self-expandable nitinol stent. Procedures were performed in a sterile catheterization laboratory. Standard balloon valvuloplasty was performed, then the bioprosthetic valve was inserted via the femoral artery; the subclavian artery was used if femoral access was impossible. A cardiac pacing catheter was systematically placed in the right ventricle via the femoral vein, and removed at the end of the procedure if no conduction anomaly was observed during procedure. Two different valve sizes were used (26 or 29 mm), depending on the size of the native aortic annulus. The femoral arterial access was closed with a percutaneous closure system (or surgically for subclavian access). All patients received heparin during procedure and 6 months’ post-procedural dual antiplatelet therapy. All major procedural adverse events were identified as recommended by VARC-28. Intracardiac electrophysiology study was performed systematically during the first week after TAVI implantation and a pacemaker was implanted in case of persistent serious conduction anomaly (left bundle branch block or HV period >55 ms).

**Follow-up**

All patients underwent systematic 1 and 6 month clinical assessment. Blood BNP level was measured at 1 month and complete echocardiography (as described for baseline assessment) was performed at 6 months. PH was again defined as PASP >40 mmHg. Any episode of atrial fibrillation or need for new pacemaker was noted. Any readmission for cardiac failure or death (cardiovascular or non-cardiovascular mortality as defined by VARC-28) was reported after 30 days. Prescribed medications were reported, including diuretics, beta-blockers and Angiotensin-Converting-Enzyme (ACE) inhibitors.

**Group identification**

Patients were divided into 2 groups according to PASP at 6 months post-TAVI: one group without PH (PASP ≤ 40 mmHg, considered as a favorable result) and the other with PH (PASP >40 mmHg, considered as an unfavorable result).

**Statistical analysis**

Qualitative values were expressed as a (percentage) and quantitative values as mean ± SD. Patient data were compared by Student’s t-test for continuous variables and chi-squared test for categorical variables. A p-value of 0.05 was considered significant. Stepwise logistic regression analysis was performed, including all variables with p<0.05 on univariate analysis, and determined predictive values for post-TAVI PH. Mortality and survival rates were presented as Kaplan-Meier curves. Statistical analyses were performed with Stat View 5.0 software (SAS Institute Inc., Cary, NC).

**Results**

In total, 58 were studied during the inclusion period from November 2008 to December 2010.

Mean follow-up was 20 ± 7 months.

**Global results**

Patient data at baseline and follow-up, and the principal TAVI results and complications, are presented in Table 1. Missing data were only noted for BNP measures.

Patients presented high perioperative risk (mean EuroSCORE of 24% ± 14 and STS score of 8% ± 7) and were elderly (83 ± 7 years). Baseline echocardiography showed normal LVEF (57% ± 10.3); 40% of patients presented PH, as defined above, at inclusion.

TAVI was successful in 100% of patients: femoral access was used in 81% of procedures. Twenty six percent of patients showed conduction anomalies during TAVI, 7% major bleeding events, 2% pericardial tamponade and 7% stroke events.

Follow-up found overall clinical improvement, with significantly reduced NYHA scores. No significant results noted for BNP analysis.

Echocardiography showed excellent aortic results, with significantly reduced mean aortic gradient and increased indexed aortic valve area and velocity ratio. LVEF remained unchanged.

Absolute reduction concerning PASP values 6 months after TAVI was non-significant (45 to 42mmHg) and 43% of patients presented criteria of PH, as defined in Methods Section, 6 months after TAVI. More interestingly, individual PASP evolution patterns did not systematically consist of descending slopes, as might be expected, but remained elevated, or even increased in a certain number of cases (Figure 1).

The degree of Mitral Regurgitation (MR) significantly decreased. Aortic regurgitation did not significantly change, and was low-grade (≤ II) in 98% of cases.

Reduction in atrial fibrillation was non-significant (36 to 29%). Pacemaker implantation was required in 45% of patients after TAVI, although only 14% needed permanent pacing.

There were 13 deaths (22%) during follow-up, 54% being due to cardiovascular causes. Twenty two percent of patients were readmitted for cardiac failure. Medical treatment was optimal.

**Analysis by 2 groups**

Patients were divided into 2 groups according to PASP values 6 months after TAVI. Results are presented in Table 2. Follow-up was identical in both groups.

PASP levels were similar before TAVI in both groups and higher after TAVI in the PH group (53 vs. 32mmHg). 25 patients presented criteria for post-TAVI PH (43% of the total population): persistent PH in 14 cases and new onset in 11 cases. Four clinical situations can
be identified by analyzing presence or absence of PH before and after TAVI Table 3.

Baseline characteristics were similar for age, history of chronic obstructive pulmonary disease and pre-operative severity (EuroSCORE and STS score). Patients with PH were significantly more often female and more frequently had history of myocardial infarction. Baseline LVEF was similar in both groups (56 and 58% respectively). Patients with PH were significantly more symptomatic.

Echocardiographic findings were similar, with excellent results on the aortic valve and LVEF. Elevated PASP levels were consistent with LV diastolic dysfunction (significantly higher left atrial area before and after TAVI, E/A and E/E’ ratios could be interpreted in two-thirds of patients and appeared consistent with elevated diastolic LV pressures after TAVI; E/A higher than 2 or E/E’ higher than 15).

Mitril regurgitation was significantly more severe both before and after TAVI in the PH group, with post-TAVI MR grade III in 3 cases, and its evolution was more often unfavorable (36% worsened, 36% unchanged and 28% improved in the PH group, versus 21%, 49% and 30% respectively in the non-PH group). Atrial fibrillation was significantly more frequent in the PH group at baseline (56% vs. 21%) and post-TAVI (48% vs. 15%). Pacemakers were significantly more frequent in the PH group both before (20% vs. 6%) and after TAVI (72% vs. 45%), with more frequent permanent pacing (20% vs. 9%). Stepwise logistic regression applied to the variables identified as significant on univariate analysis showed that pre-TAVI atrial fibrillation was the only independent predictive factor for post-TAVI PH (p=0.006).

Proportions of the predictive factors identified after univariate analysis were measured for each of the 4 clinical situations and presented in Table 3; due to the small number of patients in each group, no statistic significance could be calculated. However descriptive analysis can be performed and atrial fibrillation appears more frequent in the group with persisting PH, and post-TAVI MR was more severe in the group with new-onset PH.

Figure 2 shows the Kaplan-Meier curves for overall and cardiovascular survival. Mortality from any cause was similar in both groups (24% and 21% for the groups with and without PH, respectively); however, deaths in the PH group were exclusively from cardiovascular causes, and cardiovascular mortality was therefore significantly higher in that group (24% versus 3%) and cardiovascular survival significantly poorer (76% versus 97% at 3 years). Non-cardiovascular deaths in the non-PH group were due to terminal cancer in nearly half of the cases.

Figure 1: Outcome of Pulmonary Arterial Systolic Pressures before and 6 months after TAVI.
Clinical implications and prognosis of PH after TAVI

The present overall mortality rates were similar to those of the PARTNER trial 3, where 1-year mortality from any cause was 30.7%, and 20.5% for cardiovascular causes. Pre-procedural PH was reported to be a factor of poor prognosis in aortic stenosis, in surgical series6 and in a recent TAVI trial5. The present findings complete these results, with presence of PH in 43% of patients at 6 months; moreover, PH persisted in 14 cases and was new in 11 cases. To our knowledge, no other study has developed this fact.

Table 2: Patient characteristics and outcomes depending on the presence or absence of Pulmonary Hypertension 6 months after TAVI.

| Group without PH at 6M | Group with PH at 6M | p |
|-----------------------|---------------------|---|
| **Patient characteristics** | | |
| Distribution in TAVI population | 33 (57%) | 25 (43%) | - |
| Follow-up | 20 ± 7 | 20 ± 8 | 0.84 |
| Male/Female | 18/15 | 11/14 | 0.03 |
| Age, y | 83 ± 7 | 82 ± 7 | 0.62 |
| Hypertension | 23 (70%) | 17 (68%) | 0.06 |
| Diabetes | 9 (27%) | 7 (24%) | 0.03 |
| Pulmonary chronic obstructive disease | 7 (21%) | 6 (24%) | 0.07 |
| History of myocardial infarction | 4 (12%) | 5 (20%) | 0.02 |
| History of coronary by-pass | 14 (42%) | 7 (28%) | 0.007 |
| EuroScore | 23 ± 12 | 25 ± 6 | 0.73 |
| STS score | 8 ± 8 | 7 ± 5 | 0.19 |
| Creatinine clearance, mL/min | 59 ± 23 | 60 ± 18 | 0.38 |
| NYHA at baseline | 2/11/13/7 | 1/6/14/4 | 0.01 |
| NYHA after TAVI | 19/9/4/1 | 4/9/6/6 | < 0.0001 |
| Atrial fibrillation at baseline | 12 (21%) | 14 (56%) | < 0.0001 |
| Atrial fibrillation after TAVI | 5 (15%) | 12 (48%) | < 0.0001 |
| Pacemaker at baseline | 2 (6%) | 5 (20%) | 0.002 |
| Pacemaker after TAVI | 5 (15%) | 18 (72%) | < 0.0001 |
| **Echocardiography** | | |
| LVEF at baseline | 56 ± 11 | 58 ± 10 | 0.5 |
| LVEF after TAVI | 58 ± 11 | 58 ± 14 | 0.94 |
| Indexed m²/aortic valve area after TAVI, cm | 1.07 ± 0.4 | 0.98 ± 0.34 | 0.22 |
| Velocity ratio after TAVI | 0.57 ± 0.15 | 0.56 ± 0.22 | 0.17 |
| Mean gradient after TAVI, mmHg | 9 ± 5 | 7 ± 3 | 0.1 |
| Aortic regurgitation grade after TAVI, 0/I/II/III/IV | 8/16/8/10 | 7/14/4/0/0 | 0.37 |
| Mitral regurgitation grade at baseline, 0/I/II/III/IV | 4/2/18/0/0 | 3/10/12/0/0 | 0.001 |
| Mitral regurgitation grade after TAVI, 0/I/II/III/IV | 7/18/8/0/0 | 6/8/8/3/0 | 0.001 |
| PASP at baseline, mmHg | 42 ± 13 | 48 ± 18 | 0.17 |
| PASP after TAVI, mmHg | 32 ± 6 | 53 ± 11 | < 0.0001 |
| Left atrial² area at baseline, mm² | 25 ± 6 | 29 ± 9 | 0.02 |
| Left atrial² area after TAVI, mm² | 23 ± 5 | 30 ± 8 | < 0.0001 |

Table 3: Distribution of predictive factors for Pulmonary Hypertension.

| PH status | No pulmonary hypertension | Improving pulmonary hypertension | New pulmonary hypertension | Persisting pulmonary hypertension |
|-----------|---------------------------|----------------------------------|---------------------------|----------------------------------|
| n | 23 | 10 | 11 | 14 |
| History of myocardial infarction, % (n) | 13 (3) | 10 (1) | 18 (2) | 21 (3) |
| LVEF > 50%, % (n) | 78 (18) | 50 (5) | 73 (8) | 71 (10) |
| LA>LV<50%, % (n) | 22 (5) | 50 (5) | 27 (3) | 29 (4) |
| Pacemaker after TAVI, % (n) | 39 (9) | 60 (6) | 73 (8) | 71 (10) |
| PM dependency, % (n) | 4 (1) | 20 (2) | 18 (2) | 21 (3) |
| Baseline atrial fibrillation, % (n) | 9 (2) | 50 (5) | 55 (6) | 57 (8) |
| Atrial fibrillation after TAVI, % (n) | 9 (2) | 30 (3) | 36 (4) | 57 (8) |
| Baseline mitral insufficiency 0/I/II/III/IV, n | 4/16/3/0/0 | 0/5/5/0/0 | 0/4/7/0/0 | 3/6/5/0/0 |
| Mitral insufficiency after TAVI 0/I/II/III/IV, n | 6/12/5/0/0 | 1/8/3/0/0 | 3/2/3/3/0 | 3/6/5/0/0 |

Discussion

Outcome of PH after TAVI

Pulmonary hypertension is frequently associated with aortic stenosis. Frequency is quite variable in the literature, as the definition of PH differs from one study to another. The present series showed a 40% rate of PH at baseline, which is similar to the results of the PARTNER trial 3. Baseline PH was more frequent in a recent trial comparing evolution between surgery, TAVI and balloon valvuloplasty 5, at 68.2% (for PASP >40 mmHg); this can be explained by the specific design of that study (groups matched for baseline PASP). In the present study, the reduction in pulmonary pressure after TAVI was non-significant (from 45 to 42 mmHg); this could be explained by lower baseline PASP in our study (mean 45 mmHg). Significant decrease in PASP was reported in recent TAVI trials 4-5: from 66.1 mmHg at 1 week to 44.8 mmHg at 12 months 5. The present study modulates conveys a nuance to these results, with presence of PH in 43% of patients at 6 months; moreover, PH persisted in 14 cases and was new in 11 cases. To our knowledge, no other study has developed this fact.

(43% of non-cardiovascular deaths), the others being essentially due to septic causes remote from the TAVI procedure. Therefore, non-cardiovascular deaths due to cancer in the non-PH group might have been avoided by a better patient selection before TAVI and should not impair the significance of greater cardiovascular mortality found in the PH group. Moreover, patients presenting post-TAVI PH were significantly more frequently admitted for cardiac failure (32%), although they were effectively treated and received significantly more medication (100% diuretics, 68% ACE inhibitors and 56% beta-blockers).
term mortality (past the 30 first days) is usually strongly determined by non-cardiac deaths, especially from respiratory causes [12]. Patients in the PH group died exclusively from cardiac causes (24% mortality rate). Moreover, clinical evolution was less favorable, as these patients were more symptomatic, with more frequent admission for cardiac failure and more intensive medical treatment during follow-up. BNP levels did not differ significantly between groups; this is explained by the small number of samples performed. It is difficult to predict the risk for post-TAVI PH in order to better select patients before TAVI. Indeed, the only predictive factor seems to be pre-TAVI atrial fibrillation. Moreover, prognosis was shown to be improved in the subgroup of patients with post-TAVI PH, when comparing surgical to medical treatment at 1 month and 5 years [13,14]. In the PARTNER trial 3, TAVI provided better results than medical treatment in all groups, including in the PH group. These patients should therefore be surveyed even more closely than usual for signs of cardiac failure, and should receive intensified medical treatment: i.e., diuretics, ACE inhibitors and beta blockers.

**Predictive factors for post-TAVI PH**

**Aortic results and LV systolic function:** These elements cannot explain the elevation of pulmonary pressure, as results on the aortic valve were excellent and post-TAVI LVEF was normal and stable. Results were similar to those in recent trials 2-4 and similar in both groups.

**History of myocardial infarction:** Although myocardial infarction was more frequent in the PH group, systolic dysfunction cannot explain the elevation of PASP, as LVEF was normal in both groups. Myocardial scarring, however, could induce diastolic dysfunction and elevate pulmonary pressure [15].

**Pacemaker implantation:** Pacemakers are more often required after Corevalve TM implantation (Medtronic CV, Irvine, CA), possibly due to deeper prosthetic valve insertion beyond the non-coronary cusp [16]. The present rate of pacemaker implantation, however, was higher than usual in the literature, at 45% of cases after TAVI (compared to 25% in the FRANCE registry); this can be explained by the protocol applied in our center during this study (described in the Method section). This approach was not associated with higher postoperative mortality or morbidity. However, pacemaker presence was significantly more frequent in the PH group. A ventricular pacing effect on LV diastolic pressure is questionable, as long-term ventricular pacing was found to be associated with reduced LV systolic function and impaired relaxation [17]. However, indications for pacemaker were generally transitory conduction abnormalities (pacemaker dependency was low, at 9-20%); ventricular desynchronisation therefore seems unlikely. Moreover no significant traumatic tricuspid regurgitation was noted.

**Mitral regurgitation:** MR was significantly more severe in the PH group. It is known to be associated with aortic stenosis in two thirds of patients, with 27-48% moderate-to-severe MR in patients undergoing TAVI [18]. The present study found a 36% rate of pre-TAVI MR of grade 2 or more. Several studies addressed change in MR after TAVI [19]. Functional MR is expected to regress after TAVI but prosthetic valve implantation, especially with CorevalveTM (Medtronic CV, Irvine, CA), has been suspected of inducing MR by affecting the left ventricular outflow track because of its deep insertion under the aortic annulus or by impacting anterior mitral leaflet motion. Results are
controversial: no correlation was found by Tzikas, with a mean insertion depth of 8mm; in contrast, a more recent study found a significant association between the depth of the aortic prosthesis (7.6mm versus 9.4 mm for the mean distance between the ventricular end and right coronary cusp) and aggravated MR [20,21]. In the present study, close examination of insertion depth revealed no correlation, especially for the 3 patients presenting severe MR (grade 3) (results not developed).

Atrial fibrillation: Atrial fibrillation at baseline and during follow-up was significantly more frequent in the PH group. Moreover, pre-TAVI atrial fibrillation emerged as an independent predictive factor for post-TAVI PH. Although rapid atrial fibrillation can be a cause of LV dysfunction, atrial fibrillation as such is more often a consequence [22]. Presence and severity of diastolic dysfunction were shown to be independently predictive of primary non-valvular atrial fibrillation in the elderly [23]. Greater prevalence of atrial fibrillation in the PH group therefore reflects the greater severity of LV diastolic dysfunction in these patients. The substrate for atrial fibrillation has been shown to be atrial fibrosis; myocardial investigation might therefore prove interesting to explore the relevance of myocardial fibrosis [24].

Diastolic dysfunction: Echocardiographic evaluation of LV diastolic function was difficult in this population and limited by a certain number of comorbidities (atrial fibrillation, pacemaker implantation, calculations extending to the mitral annulus). However, results were consistent with high LV diastolic pressure in the PH group. Myocardial fibrosis (due to a necrotic scar or to age) could possibly explain this diastolic dysfunction and elevated pulmonary pressures.

Differentiating new PH and persisting PH?: Table 3, analyzing the 4 clinical situations identified by presence or absence of PH before and after TAVI, shows equivalent proportions of predictive factors from univariate analysis, especially when comparing the clinical situations of new or persisting PH and improving PH after TAVI. Numbers in each group are small; however post-TAVI MR appears more severe in the new PH group and post-TAVI atrial fibrillation more frequent in the persistent PH group, both results probably reflecting greater LV diastolic dysfunction.

Myocardial fibrosis?: Several recent studies measured myocardial fibrosis in this specific population, showing that its presence (identified by late gadolinium enhancement on myocardial MRI) was associated with reduced postoperative survival and its absence with significant postoperative improvement in LVEF and NYHA score [25,26]. Complementary myocardial exploration would therefore be interesting in this population in order to explore the implication of diastolic dysfunction in post-TAVI PH.

Study limitations: The present study was limited by the relatively small number of cases, in a population of elderly and complex patients with multiple comorbidities. However, it reflects the reality of the patient population presently treated by TAVI.

Conclusion

In conclusion, PH is frequently present after TAVI and is associated with poorer clinical status and cardiovascular prognosis. Clinicians should be aware of this possible evolution, in order to monitor patients even more closely and intensify post-procedural medical treatment. A certain number of predictive factors were significantly associated with elevation of pulmonary pressure, but only atrial fibrillation was identified as an independent predictive factor on multivariate analysis. These results are specific to the complex population of patients currently treated by TAVI; further studies are necessary, and especially complementary myocardial investigation to explore myocardial fibrosis.

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