

# Analysis of the Incidence and Clinical and Echocardiographic Predictors of Paravalvular Aortic Regurgitation after Transcatheter Aortic Valve Implantation

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## ABSTRACT

**Background:** The incidence of paravalvular aortic regurgitation (PAR) seems higher among patients submitted to transcatheter aortic valve implantation and its potential association with an increased late mortality has raised concerns in the scientific community. Our objective was to evaluate the incidence and clinical impact of PAR and establish PAR predictors in our patient population. **Methods:** Between July/2009 and February/ 2013, 112 patients were submitted to transcatheter aortic valve implantation. The degree of PAR after the procedure was assessed according to the VARC 2 criteria. The population was divided into no/mild PAR group and moderate/severe PAR group. **Results:** Mean age was  $82.5 \pm 3.9$  years, 58.9% were female and the logistic EuroSCORE was  $23.6 \pm 13.4$ . There was a decrease in the mean systolic gradient ( $54.7 \pm 15.3$  mmHg vs  $11.7 \pm 4$  mmHg;  $P < 0.01$ ) and a gain in the aortic valve area ( $0.66 \pm 0.15$  cm<sup>2</sup> vs  $1.8 \pm 0.3$  cm<sup>2</sup>;  $P < 0.01$ ). At the end of the procedure 46.4% did not have PAR, and mild or moderate PAR was observed in 42% and 11.6% of the patients. No patient presented severe PAR. Multivariate analysis identified male gender [odds ratio (OR) 5.85, confidence interval (CI) 1.29-26.7;  $P = 0.022$ ], previous percutaneous aortic valvuloplasty (OR 18.44, CI 2.30-147.85;  $P = 0.006$ ), ejection

## RESUMO

### Análise da Incidência e Preditores Clínicos e Ecocardiográficos do Refluxo Paraprotético Aórtico após o Implante de Prótese Aórtica Transcateter

**Introdução:** A incidência de refluxo paraprotético (RPP) parece maior entre os pacientes submetidos a implante de prótese aórtica transcater e sua potencial associação com aumento da mortalidade tardia tem suscitado preocupação na comunidade científica. Nosso objetivo foi avaliar a incidência e o impacto clínico e estabelecer preditores do RPP em nossa casuística. **Métodos:** Entre julho de 2009 e fevereiro de 2013, 112 pacientes foram submetidos a implante de prótese aórtica transcater. O grau do RPP pós-procedimento foi avaliado segundo os critérios do VARC 2. Dividiu-se a população em grupo RPP ausente/RPP discreto e grupo RPP moderado/RPP grave. **Resultados:** A média da idade foi de  $82,5 \pm 3,9$  anos, 58,9% eram do sexo feminino e o EuroSCORE logístico foi de  $23,6 \pm 13,4$ . Houve queda do gradiente sistólico médio ( $54,7 \pm 15,3$  mmHg vs.  $11,7 \pm 4$  mmHg;  $P < 0,01$ ) e ganho da área valvar aórtica ( $0,66 \pm 0,15$  cm<sup>2</sup> vs.  $1,8 \pm 0,3$  cm<sup>2</sup>;  $P < 0,01$ ). Ao final do procedimento, 46,4% não apresentaram RPP, e RPP discreto ou moderado foi observado em 42% e 11,6% dos pacientes. Nenhum paciente

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fraction < 35% (OR 4.160, CI 1.014-17.064; P = 0.048) and the presence of severe pulmonary hypertension (OR 7.649, CI 1.86-31.51; P = 0.005) as independent predictors of moderate/severe PAR. **Conclusions:** The incidence of moderate/severe PAR was low and comparable to other studies. Male gender, history of prior percutaneous aortic valvuloplasty, presence of severe pulmonary hypertension and severe left ventricular dysfunction were independent predictors of this complication.

**DESCRIPTORS:** Aortic valve insufficiency. Aortic valve stenosis. Cardiac catheters. Heart valve prosthesis implantation.

In recent years, the implantation of a transcatheter aortic valve prosthesis has become the treatment of choice for patients with severe symptomatic aortic stenosis considered inoperable,<sup>1</sup> and an effective alternative in patients at high surgical risk.<sup>2</sup>

However, the incidence of paravalvular aortic regurgitation (PAR) appears to be higher among patients submitted to transcatheter aortic valve implantation than after surgical aortic valve replacement,<sup>1,2</sup> and its potential association with increased late mortality<sup>3</sup> has raised concern in the international scientific community; PAR is considered the downfall of transcatheter aortic prosthesis implantation.<sup>4</sup>

The present study aimed to evaluate the incidence, severity, and clinical impact of PAR in patients undergoing transcatheter aortic prosthesis implantation at two institutions in the State of São Paulo, Brazil, and to try to establish the clinical and echocardiographic predictors of this serious problem.

## METHODS

### Subjects and procedure

This retrospective study included all symptomatic patients with severe aortic stenosis, considered to be at high surgical risk/inoperable, submitted to transcatheter aortic prosthesis implantation at Instituto de Cardiologia Dante Pazzanese and at Hospital do Coração da Associação do Sanatório Sírio between June 2009 and February 2013.

As part of the pre-intervention assessment, patients underwent computed tomography, angiography of the heart, aorta, and iliac arteries; coronary angiography; and transthoracic echocardiography. Based on the results of these tests, and after discussing with the local heart team, the access route was chosen, and the type and diameter of the prosthesis to be implanted was established. Three types of prosthesis were used:

apresentou RPP grave. A análise multivariada identificou sexo masculino [odds ratio (OR) 5,85, intervalo de confiança (IC) 1,29-26,7; P = 0,022], valvoplastia aórtica percutânea prévia (OR 18,44, IC 2,30-147,85; P = 0,006), fração de ejeção < 35% (OR 4,160, IC 1,014-17,064; P = 0,048) e presença de hipertensão pulmonar grave (OR 7,649, IC 1,86-31,51; P = 0,005) como preditores independentes de RPP moderado/grave. **Conclusões:** A incidência de RPP moderado/grave foi baixa e comparável à de outras casuísticas. Sexo masculino, antecedente de valvoplastia aórtica percutânea prévia, presença de hipertensão pulmonar grave e disfunção ventricular esquerda grave foram preditores independentes dessa complicação.

**DESCRIPTORES:** Insuficiência da valva aórtica. Estenose da valva aórtica. Cateteres cardíacos. Implante de prótese de valva cardíaca.

CoreValve® (Medtronic – Minneapolis, USA) by transfemoral, trans-subclavian, or transaortic approach; SAPIEN XT™ (Edwards Lifesciences – Irvine, California, United States), by transfemoral or transapical approach; and Acurate TF™ (Symetis Inc. – Geneva, Switzerland) by transfemoral approach.

All procedures were performed under general anesthesia and guided by transesophageal echocardiography. After left ventricular catheterisation, aortic balloon valvuloplasty was performed in cases in which the SAPIEN XT™ and Acurate TF™ prostheses were used or, when necessary, in cases in which the CoreValve® prosthesis was used. Subsequently, the prosthesis was implanted, and post-dilation was performed at the surgeon's discretion.

### Definitions

The pre-intervention clinical variables followed the definitions published by the Society of Thoracic Surgeons,<sup>5</sup> and surgical risk and possible post-intervention complications were determined in accordance with the logistic EuroSCORE.<sup>6</sup>

Transthoracic echocardiography was used to define the left ventricular end-systolic and end-diastolic diameter, left ventricular ejection fraction, aortic annulus diameter, the diameter of the sinus of Valsalva, the ascending aorta diameter, the aortic valve area, the maximum and mean systolic gradients, the severity of aortic valve calcification, and the prosthetic valve area.

The degree of PAR after the procedure was evaluated by transthoracic echocardiography performed by one of three experienced echocardiographers designated as members of the heart team and according to the criteria proposed by the Valve Academic Research Consortium – 2 (VARC 2),<sup>7</sup> classified as mild, moderate, or severe PAR using semi-quantitative and quantitative parameters.<sup>4,7,8</sup>

The study population was divided into two groups, according to the occurrence of post-procedure PAR: absent PAR/mild PAR and moderate PAR/severe PAR.

Device success was considered when a single prosthesis was implanted properly and final results showed absence of prosthesis-patient mismatch, mean aortic transvalvular gradient < 20 mmHg, peak velocity < 3 m/s, and mild aortic regurgitation at the maximum.<sup>7</sup>

### Statistical Analysis

Continuous variables were shown as means and standard deviations, and categorical variables as frequencies and percentages, compared, respectively, by the chi-squared test and Student's *t*-test.

A Cox logistic regression model was used to determine independent predictors of moderate/severe PAR after transcatheter aortic valve implantation, including variables with P-values  $\leq 0.2$  in the univariate model.

Data were analyzed using SPSS, version 20 (SPSS Inc. – Chicago, USA). P-values < 0.05 were considered statistically significant.

## RESULTS

### Characteristics of the population and the procedure

Between June 2009 and February 2013, a total of 182 patients with symptomatic severe aortic stenosis were evaluated for transcatheter aortic valve implantation. Of these, 112 patients (62%) underwent transcatheter aortic valve implantation at Instituto Dante Pazzanese de Cardiologia ( $n = 96$ , 86%) and at the Hospital do Coração da Associação do Sanatório Sírio ( $n = 16$ , 14%).

Basal clinical and echocardiographic characteristics of the 112 patients are shown in Table 1. The mean age of patients was  $82.5 \pm 3.9$  years, and the majority (58.9%) were female. The mean logistic EuroSCORE was  $23.6 \pm 13.4$  and 88 (79%) were in functional class III – IV of the New York Heart Association (NYHA) criteria before the intervention.

The femoral vein was used in 91% of the patients, followed by transapical (6%), transaortic (2%), and subclavian (1%) routes. The CoreValve® prosthesis was used in 76 patients (68.8%), whereas the Sapien XT™ was used in 21 (18.8%), and the Acurate TF™, in 15 (13.4%).

The maximum transaortic gradient before the procedure was  $88 \pm 24.3$  mmHg and the mean was  $54.7 \pm 15.3$  mmHg, whereas the mean aortic valve area was  $0.66 \pm 0.15$  cm<sup>2</sup>. There was a decrease in the mean systolic gradient (pre =  $54.7 \pm 15.3$  mmHg vs. post =  $11.7 \pm 4$  mmHg;  $P < 0.01$ ) and a gain in aortic valve area (pre =  $0.66 \pm 0.15$  cm<sup>2</sup> vs. post =  $1.8 \pm 0.3$  cm<sup>2</sup>;  $P < 0.01$ ) immediately after device implantation.

Device success was achieved in 94 patients (83.9%). There were two deaths during the procedure (1.8%), and five cases (4.5%) needed a second prosthesis due to inappropriate positioning of the first.

Immediately after prosthesis implantation, 38 patients (33.9%) required post-dilation to reduce PAR, which occurred in two-thirds of the patients. At the end of the procedure, 52 patients (46.4%) had no PAR and 47 (42%) had mild PAR, while moderate PAR was observed in 13 patients (11.6%). No patients had severe PAR.

Among the patients who developed moderate/severe PAR, the incidence of previous aortic valvuloplasty was higher (23.1% vs. 5.1%;  $P = 0.049$ ). Additionally, patients in this group had smaller aortic valve area ( $0.67 \pm 0.15$  cm<sup>2</sup> vs.  $0.59 \pm 0.09$  cm<sup>2</sup>;  $P = 0.007$ ), and left ventricular ejection fraction was also lower ( $58.2 \pm 12.6\%$  vs.  $48.6 \pm 15.1\%$ ;  $P = 0.013$ ) at the pre-intervention echocardiography. There was no difference between the groups regarding mean transaortic gradient, aortic annulus diameter, severity of aortic valve calcification, and incidence of bicuspid aortic valve.

Patients in both groups did not differ regarding the type of prosthesis used and the amount of contrast or procedure duration. Overall 30-day mortality of patients included in this study was 14.3%, with no statistical difference between groups. After the first 30 days, mortality from all causes, considering only patients who were discharged from the hospital, was 9.4%. The mid-term follow-up ( $16 \pm 11$  months) showed no difference in mortality between the groups (Table 2).

Multivariate analysis identified the following independent predictors of moderate/severe PAR: male gender (odds ratio [OR] 5.85; confidence interval [CI]: 1.29 to 26.7;  $P = 0.022$ ), aortic valvuloplasty prior to the percutaneous procedure (OR: 18.44; CI: 2.30 to 147.85;  $P = 0.006$ ), ejection fraction < 35 % (OR: 4.160; CI: 1.014 to 17.064;  $P = 0.048$ ), and presence of severe pulmonary hypertension (OR: 7.649; CI: 1.86 to 31.51;  $P = 0.005$ ). No variables of the procedure were associated with the occurrence of this complication.

## DISCUSSION

The most important finding of the present study was that, although the occurrence of transcatheter aortic valve post-implantation PAR is common (53.6%), most cases are mild. In this study, there were no cases of severe PAR, and moderate PAR did not result in poor clinical outcome in the mid-term follow-up.

The incidence of moderate/severe PAR in the present patients (11.6%) was similar to that observed in the Placement of Aortic Transcatheter Valve Trial (PARTNER),<sup>1,2</sup> a randomized study in which the incidence in the A and B cohorts was 12.2% and 11.8%, respectively. Regarding the high incidence of mild PAR (42%), several international registries have shown similar rates.<sup>9-11</sup>

**TABLE 1**  
Basal clinical and echocardiographic characteristics

	Total (n = 112)	Absent/mild paravalvular aortic regurgitation (n = 99)	Moderate/severe paravalvular aortic regurgitation (n = 13)	P-value
Age, years	82.5 ± 3.9	82.8 ± 6.1	79.9 ± 8.9	0.28
Female gender, n (%)	66 (58.9)	61 (61.6)	5 (38.5)	0.1
Body mass index, kg/m <sup>2</sup>	25.7 ± 3.9	24.7 ± 6.2	25.9 ± 5.4	0.5
Logistic EuroSCORE	23.6 ± 13.4	23.1 ± 12.8	27.7 ± 17.8	0.2
Previous coronary artery bypass graft surgery, n (%)	24 (21.4)	21 (21.2)	3 (23.1)	> 0.99
Previous valvuloplasty, n (%)	8 (7.1)	5 (5.1)	3 (23.1)	0.049
Chronic obstructive pulmonary disease, n (%)	14 (12.5)	12 (12.1)	2 (15.4)	0.67
Severe pulmonary hypertension, n (%)	37 (33)	30 (30.3)	7 (53.8)	0.1
Aortic valve area, cm <sup>2</sup>	0.66 ± 0.15	0.67 ± 0.15	0.59 ± 0.09	0.007
Mean pre-implantation transaortic gradient, mmHg	54.7 ± 15.3	55.2 ± 14.9	50.4 ± 18.1	0.29
Left ventricular ejection fraction, %	57.1 ± 13.2	58.2 ± 12.6	48.6 ± 15.1	0.013
Aortic annulus diameter, mm	22.4 ± 1.7	22.4 ± 1.7	22.4 ± 1.8	0.9
Left ventricular end-systolic diameter, mm	34.7 ± 9.1	33.7 ± 8.1	38.6 ± 17	0.39
Left ventricular end-diastolic diameter, mm	51.4 ± 7.1	50.1 ± 55.6	55.6 ± 9.9	0.13
Valsalva sinus diameter, mm	31.7 ± 4.7	31.6 ± 4.8	33.2 ± 2.4	0.29
Ascending aorta diameter, mm	34.5 ± 4	34.5 ± 4.4	34.5 ± 3.5	0.96
Severe aortic valve calcification, n (%)	47 (42)	41 (41.4)	6 (46.2)	0.73
Bicuspid aortic valve, n (%)	5 (4.5)	5 (5.1)	0	> 0.99
Mean post-implantation transaortic gradient, mmHg	11.7 ± 4	11.8 ± 4	10.8 ± 4.4	0.16
Prosthetic valve area, cm <sup>2</sup>	1.8 ± 0.3	1.8 ± 0.26	1.9 ± 0.25	0.4

**TABLE 2**  
Types of valve used and main characteristics of the procedure

	Total (n = 112)	Absent/mild paravalvular aortic regurgitation (n = 99)	Moderate/severe paravalvular aortic regurgitation (n = 13)	P-value
Types of valve, n (%)				0.76
CoreValve®	76 (6.8)	67 (67.7)	10 (76.9)	
Sapien XT™	21 (18.8)	19 (19.2)	2 (15.4)	
Acurate TF™	15 (13.4)	14 (14.1)	1 (7.7)	
Contrast volume, mL	145.1 ± 68.4	145.9 ± 71.7	139.2 ± 35.1	0.75
Duration of procedure, minutes	109 ± 41.5	107.2 ± 40.5	124.5 ± 49.2	0.24
30-day mortality, n (%)	16 (14.3)	14 (14.1)	2 (15.4)	> 0.99
Mid-term mortality, n (%)	9 (8)	8 (8.1)	1 (7.7)	> 0.99

It has been speculated that the high incidence of PAR described after transcatheter aortic valve implantation, a result of the incomplete apposition of the prosthesis in the aortic annulus, may be caused by the

heterogeneity of calcium distribution in the leaflets and annulus, or by the incorrect selection of the prosthesis diameter due to inadequate annulus measurement or the presence of extremely oval-shaped aortic annuli.<sup>4,12</sup>

One of the main predictors of PAR described in the literature is the low ratio between prosthesis diameter and annulus diameter assessed by echocardiography (or cover index).<sup>13</sup> In a study published in 2009, Detaint et al.<sup>13</sup> reported the absence of PAR moderate/severe in patients with cover index > 8%. Therefore, it is believed that the oversizing of the annulus diameter when choosing the prosthesis could be a good measure to prevent significant PAR after implantation. Another way to minimize the occurrence of this complication would be to choose the prosthesis diameter based on the tomography, not on the transthoracic echocardiography, as some recent studies have shown this method to be more accurate in predicting the size of the annulus and the valve area.<sup>14-16</sup> Currently, it is recommended to choose a prosthesis with a diameter at least 1 mm larger than the mean annulus diameter, or area 10% larger than the annulus area measured by multiple-slice computed tomography.<sup>15</sup> However, it is worth mentioning that oversizing the prosthesis is not devoid of risk, as it can lead to annulus rupture.<sup>17</sup>

In the present series, the only echocardiographic predictor of PAR identified was the presence of severe left ventricular dysfunction (LV ejection fraction < 35%). Although the degree of calcification of leaflets and annulus was not a predictor of this event, it is worth noting that calcium assessment was performed qualitatively, based on transthoracic echocardiography evaluation. Several recent studies have used the Agatston score, defined by computed tomography, to quantitatively evaluate the valve apparatus degree of calcification. In this series, the degree of moderate/high calcification, which was more objectively assessed, emerged as an independent predictor of significant PAR.<sup>18,19</sup>

It is currently believed that the presence of PAR may have a negative impact on patient evolution.<sup>3,4,9,10,20,21</sup> In the recently published two-year evolution of the PARTNER study cohort A,<sup>3</sup> the effect of PAR on mortality was proportional to PAR severity, and even the presence of mild PAR was associated with increased late mortality. Recent meta-analysis conducted by Athappan et al.<sup>21</sup> demonstrated that moderate or severe PAR after transcatheter aortic prosthesis implantation is frequent (11.7%), and is considered an independent predictor of immediate (OR 2.95; CI: 1.73 to 5.02) as well as long-term mortality (hazard ratio [HR] 2.27; 95% CI: 1.84 to 2.81). These results suggest that measures to improve PAR may lead to improved survival in patients submitted to transcatheter aortic valve implantation. It is noteworthy that the present series had no cases of severe PAR, and that moderate PAR was not associated with worse evolution in the mid-term.

## CONCLUSIONS

In this initial experience of two national centers, the incidence of moderate/severe PAR was relatively

low and comparable to other international samples. Male gender, history of previous percutaneous aortic valvuloplasty, and presence of severe pulmonary hypertension and severe left ventricular dysfunction were identified as independent predictors of the occurrence of this complication.

## CONFLICTS OF INTEREST

Magaly Arrais is a proctor at Medtronic (Minneapolis, USA) and Edwards Lifesciences (Irvine, USA). The other authors declare to have no conflicts of interest.

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