Mechanical Valve Implants: What Are Their Long-Term Effects?

Eldys Myler Santos Marinho,[1] Júlio Martinez Martinez Santos,[2] Bruno da Silva Brito,[3] Achilles de Souza Andrade,[4] Johnnatas Mikael Lopes[2]

Universidade Federal do Vale do São Francisco (UNIVASF) – Educação Física,[1] Petrolina, PE – Brazil
Universidade Federal do Vale do São Francisco (UNIVASF) – Medicina,[2] Paulo Afonso, BA – Brazil
Universidade Federal da Paraíba - Programa de Pós-graduação em Neurociência,[3] João Pessoa, PB – Brazil
Universidade Federal da Paraíba – Medicina,[4] João Pessoa, PB – Brazil

Surgical procedures for replacing body structures through prostheses are perhaps the medical interventions that require great expertise and continuous monitoring, prolonging the lives and health of countless people. This was a theme of the research entitled "*Clinical Features and Survival Analysis of Patients after Mechanical Heart Valve Replacement, with an Emphasis on Prosthetic Valve Thrombosis*" by Tagliari et al.[1] published in volume 119, number 5 of this journal.

Among the various contributions the study brings us, some findings need further clarification so mechanical valve implant interventions can be useful clinically and in public health.

We started by analyzing the effects of the type of prosthesis on the echocardiographic parameters. The authors showed that both groups significantly increased LVEF (%).[1] However, a comparison between the groups would be necessary for better discernment by the readers, which we show in Table 1, for an evaluation of the effectiveness of this indicator. It is possible to state that the groups are statistically similar, as seen in the manuscript. However, the effect of prosthesis transplants in the mitral and mitral-aortic position is small on LVEF, as Cohen's d is less than 0.50,[2] whereas the effect of the aortic prosthesis is moderate. This raises the question: What is the implication of this difference in clinical effect on the medical management follow-up, prognosis, and physical rehabilitation of a patient? The other echocardiographic variables do not allow further analysis due to the absence of critical ratio statistical data or lack of comparability.

Another point that deserves a more in-depth analysis is survival analysis.[3] This type of analysis is applied to several events, but in a descriptive approach using Kaplan-Meyer curves, interest is always when 50% of the sample presents the outcome or some specific period, such as a year. In that study,[1] two outcomes were presented in the method: death and prosthesis thrombosis. However, in figure 3 of the study under analysis, there is no way of knowing whether the survival is the death or thrombosis outcome. The outcome appears to be about thrombosis because the supplement graphics refer to it for other independent variables. Otherwise, there is inconsistency in the organization of evidence.

It is highly interesting to present the survival curves for both outcomes and explain the median survival time, which helps in clinical practice and planning of post-surgical actions. It is also noteworthy that the Kaplan-Meyer curve only describes the survival time and that the Log Rank test specifies the difference between the survival time in the groups.[3]

In addition to the presentation of the crude survival analysis of both outcomes and their half-life times, it is also important to analyze death and valve thrombosis in the light of Cox regression to adjust the effects since it was only presented for the outcome of death. In the latter case, it was not consistent whether to apply proportional hazards Cox or time-dependent Cox.[3] It would be necessary to present the crude analysis for this outcome previously.

If the outcome was thrombosis, there are graphics in the supplement to contraindicate Cox proportional hazards. Survival graphs suggest disproportionate risks over time for the groups of independent variables analyzed. Additionally, the Hazard ratio is an effect measure that has implications on time for the outcome to occur. The relative risk interpretation was applied, which is the measure of the effect that focuses on the probability of the outcome occurring and not on time for its occurrence. This reflects on whether the finding is useful in time-dependent management or not.

Finally, some doubts can still be resolved through an adequate crude and adjusted survival analysis, such as: do the different prostheses have different effects on death and thrombosis, regardless of the demographic and clinical characteristics of the sample? What clinical variables affect outcomes controlling implant action? How can these findings be managed during patient recovery?

Keywords

Survival Analysis; Heart Valve Prosthesis Implantation; Embolism; Thrombosis; Death

Mailing Address: Johnnatas Mikael Lopes •
UNIVASF – Colegiado de Medicina – Centro de Formação Profissional de Paulo Afonso (CFPPA) – Rua da Aurora, S/N Quadra 27 Lote 3. Postal Code 48607-190, Bairro General Dutra, Paulo Afonso, BA – Brazil
E-mail: johnnataslopes2@gmail.com
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Table 1 – Comparative analysis of valve prosthesis groups and their clinical effects

	Media before	Media after	SD before	SD after	Cohen's d	CI95+	CI95-
Prosthesis position Aortic	54.1	62.6	14.7	12	0.64	54.13	62.57
Prosthesis position Mitral	54.2	56.8	2.7	13.4	0.32	54.23	56.72
Prosthesis position Mitral and aortic	55.5	61.2	14.2	12.7	0.42	55.55	61.15

SD: standard deviation; CI: confidence interval.

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Reply

Thank you for your interest in our article "Clinical and Survival Aspects of Patients after Mechanical Valve Implantation, with Emphasis on Prosthetic Valve Thrombosis"[1] demonstrated by the authors' letter. In response to the questions raised regarding the increase in ejection fraction in the different groups of prosthetic implants, our database actually lacks more detailed information for a comparative study between these groups. A more comprehensive qualitative echocardiographic evaluation would be necessary, with different measures for the different types of valve disease. This analysis would be fairly complex, given the broad presentation of the severity of heart valve diseases, whether univalvular, with the lesion being pure or mixed, with or without predominance of valve insufficiency or stenosis, and multivalvular, especially mitral and aortic involvement, with different hemodynamic presentations and degrees of severity,[2-4] prolonged time of heart valve diseases (more often seen in rheumatic patients[5]), and patients undergoing valve replacement. These many variables limit the comparison between patients. However, we can say that aortic valve lesions, whether regurgitant or stenotic, at the onset of symptoms usually evolve with a more evident improvement in the ejection fraction after valve replacement in the late follow-up of these patients, already described in the classic literature for decades. Mitral valve diseases present with different hemodynamics, either due to a preserved left ventricle in the stenotic lesion or an overestimated pseudonormal ejection fraction in the regurgitant lesion, which is more evident in symptomatic patients.[7,8] In mitral lesions, therefore, even after valve replacement, there is no significant increase in ejection fraction after prosthetic valve implantation in both stenotic and regurgitant lesions. Associated with this, there may be different degrees of pulmonary arterial hypertension, with or without right ventricular dysfunction and secondary tricuspid insufficiency, where the intensity of myocardial structural alterations confer a more reserved prognosis to these patients. Advanced valve diseases, more noticeable in mitral valve pathologies and combined aortic and mitral valve, present less favorable prognoses when compared to aortic ones, with longer rehabilitation, with patients being more symptomatic, in general, which is more evident when patients already have right ventricular dysfunction.[6] Thus, the indication of valve replacement surgery as early as possible, before cardiac structural degradation, respecting the inherent surgical risks, will provide the best clinical outcomes of rehabilitation and a better prognosis in the patient's medical follow-up.[3,9] Pulmonary artery systolic pressure (PASP) seemed to us the most interesting of the echocardiographic variables for a possible analysis; however, as it is a retrospective database, we had many values not measured ("missing"), as shown in Table 1. In any case, when analyzing the group of mitral-aortic patients, the differences between PASP1, measured on the echocardiogram before valve replacement surgery, with PASP2, measured on the last echocardiogram available for the patient, showed a significant drop in values, with statistical significance only for patients with mitroaortic valve replacement (mean 40.5±13.6 pre-valve replacement vs. 32.6 ±10.2, $p<0.001$ by Student's t)

Regarding the survival analysis, in Figure 3 of the article[1], the survival curve refers to death from all causes. The Kaplan Meier curves for prosthesis thrombosis are shown in supplementary graphs 1 and 2 by gender and age group.[1] It is important to emphasize that we had only 5 patients with thrombosis in 7 events. The thrombosis event was late, occurring only after day 2200. There is no statistically relevant mass of data to reveal a difference between the mitral, aortic, or mitral aortic valve replacement groups. Median survival was not reached in any of the three curves.

Letter to the Editor

We used a time-dependent Cox regression model for survival/death using variables judged to be clinically relevant. We found that controlling for the position of the prostheses, the only factor influencing death over time was the functional class, as shown in Table 2. In supplementary graph 6 of the published article, we had already presented similar results.[1] We did not find, throughout our article, mention of relative risk. It is not possible to perform a Cox regression for the thrombosis event due to the small number of events.

Table 1 – Results of pulmonary artery systolic pressure in a database of patients undergoing mechanical valve replacement, INC 2011-2017

Categories	Procedure	No.	Missing	Average	Median	Standard deviation	Minimum	Maximum
PASP1	Aortic	94	142	33,8	33	9.69	13	60
	Mitral	61	34	36,7	35	13.52	14	71
	Mitroaortic	79	62	40,3	40	13.28	18	84
PASP2	Aortic	122	114	30,9	28	10.62	16	90
	Mitral	60	35	35,3	32,5	11.08	22	86
	Mitroaortic	83	58	32,1	30	9.65	18	82

PASP1: pulmonary artery systolic pressure on echocardiogram performed before valve replacement; PASP2: pulmonary artery systolic pressure on echocardiogram performed after valve replacement in the patient's later follow-up.

Table 2 – Cox regression for deaths of patients undergoing mechanical valve replacement, INC 2011-2017

Time-dependent outcomes		All	HR (univariate)	HR (multivariate)
CRF	0	351 (96.7)	-	-
	1	12 (3.3)	5.00 (1.73-14.49, p=0.003)	2.44 (0.68-8.82, p=0.173)
FC	I	276 (76.0)	-	-
	II	77 (21.2)	5.20 (2.19-12.34, p<0.001)	**5.23 (2.11-12.94, p<0.001)**
	III	10 (2.8)	34.86 (13.37-90.89, p<0.001)	**39.94 (13.37-119.37, p<0.001)**
	IV	0 (0.0)	NA (NA-NA, p=NA)	NA (NA-NA, p=NA)
Procedure	Aortic	180 (49.6)	-	-
	Mitral	71 (19.6)	1.61 (0.56-4.64, p=0.382)	0.56 (0.14-2.17, p=0.398)
	Mitroaortic	112 (30.9)	1.77 (0.79-3.96, p=0.162)	2.09 (0.68-6.39, p=0.198)
Primary Etiology	Rheumatic Disease	244 (67.2)	-	-
	Bicuspid	51 (14.0)	0.47 (0.14-1.59, p=0.223)	1.00 (0.22-4.54, p=1.000)
	Calcification/Degenerative	53 (14.6)	0.34 (0.08-1.47, p=0.149)	0.56 (0.10-3.09, p=0.508)
	Undetermined	14 (3.9)	1.43 (0.33-6.16, p=0.627)	1.02 (0.18-5.77, p=0.981)
Age	Average (SD)	54.1 (10.8)	1.02 (0.99-1.06, p=0.197)	1.03 (0.99-1.08, p=0.122)

HR: hazard ratio; CRF: chronic renal failure; FC: functional class according to the New York Heart Association (I-IV).

Fábio Tagliari
Marcelo Goulart Correia
Guilherme Dalcol Amorim
Alexandre Siciliano Colafranceschi
João Manoel Pedroso
Luiz Fernando Rodrigues Junior
Thaisa Rodrigues Tagliari
Clara Weksler
Cristiane Lamas

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