Title: Impact of Preoperative Pulmonary Hypertension on Early Surgical Death in Patients Undergoing Mitral Valve Surgery due to Rheumatic Disease.

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Visual Abstract:

In patients with rheumatic heart disease who will undergo mitral valve surgery, pulmonary hypertension is associated with higher early mortality. Values above 73.5 mmHg predict higher risk.

ABSTRACT

Objective: In a population of patients undergoing cardiac surgery for rheumatic mitral valve disease, evaluate the impact of preoperative PH on early surgical mortality.

Methods: This is a prospective cohort carried out from January 1, 2017 to December 30, 2020. All patients over 18 years of age who underwent cardiac surgery to correct rheumatic mitral valve disease with functional tricuspid regurgitation in an echocardiogram performed up to 6 months before surgery were included. Systolic pulmonary artery pressure (sPAP) value was also defined by preoperative echocardiogram evaluation. The primary outcome was surgical mortality.

Results: 144 patients were included. The mean age was 46.2 (±12.3) years with 107 (74.3%) female individuals, the median left ventricular ejection fraction was 61.0% (55 - 67) and sPAP was 55.0 mmHg (46 - 74), with 45 (31.3%) individuals with right ventricular dysfunction. The predominant valve disease was mitral stenosis (74.3%). The prevalence of severe tricuspid regurgitation was 47.2%. The total in-hospital mortality was 15 (10.4%) individuals. sPAP was independently associated with early surgical death RR 1.04 (1.01 – 1.07), p = 0.003. To determine a sPAP cut-off that indicates higher mortality and help decision making in clinical practice, we performed an analysis through the ROC curve (area 0.70, p=0.012). The estimated value of 73.5mmHg has the highest accuracy in our model for predicting early mortality.

Conclusion: In patients with rheumatic heart disease who will undergo mitral valve surgery, pulmonary hypertension is associated with higher early mortality. Values above 73.5 mmHg predict higher risk and, in this part of the population, additional measures to control intraoperative and immediate postoperative pulmonary hypertension should be considered.

Keywords: pulmonary hypertension, rhematic valve disease, surgical mortality

ABBREVIATIONS

PH: Pulmonary Hypertension

sPAP: systolic pulmonary artery pressure

INTRODUCTION

Rheumatic valve disease is still a health problem worldwide, with high prevalence and high morbidity, especially in developing countries, but maintaining importance in specific populations in developed countries, where it represents the third among the causes of concomitant valve disease. Epidemiological data estimate that there were 3,604,800 cases of rheumatic heart disease in the Americas in 2017, with 22,437 deaths, representing an important socioeconomic impact.

Pulmonary hypertension (PH) may occur with the gradual progression of mitral stenosis and regurgitation (MR) in patients with rheumatic MR disease. The development of pulmonary hypertension in mitral valve disease indicates poor overall prognosis and is therefore considered an indication for early surgical intervention. Whether or not PH is associated with early surgical mortality in this specific population remais controversial. Previous studies suggest an increase in early mortality according to the degree of pulmonary hypertension, however, contemporary data show conflicting results. In addition, rheummatic patients with mitral stenosis are usually sub-represented.

The aim of this study was to evaluate the impact of preoperative pulmonary hypertension on early surgical mortality in a population of patients undergoing cardiac surgery for rheumatic mitral valve disease who have moderate to severe functional tricuspid regurgitation.

METHODS

Study design and patients

This is a prospective cohort carried out from January 1, 2017 to December 30, 2020. All patients over 18 years of age who underwent cardiac surgery to correct rheumatic mitral valve disease with moderate to severe functional tricuspid regurgitation in an

echocardiogram performed up to 6 months before surgery, at a specialized hospital in northeastern Brazil with exclusive care provided by the public health system were included. Patients with primary tricuspid valve involvement, active infectious endocarditis and associated congenital heart disease were excluded. All surgeries were performed using median sternotomy and use of cardiopulmonary bypass and aortic cross clamp.

Outcomes

The primary outcome was surgical mortality, defined as in-hospital mortality occurred in the first 30 days after the procedure. Possible predictive variables were evaluated: systolic pulmonary artery pressure (sPAP) value, defined by echocardiogram evaluation, right ventricular dysfunction, left ventricular ejection fraction and symptoms by the NYHA classification assessed at admission.

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normal distribution of continuous variables. Variables with normal distribution were described by means and standard deviations, while those with non-symmetrical distribution were described by medians and interquartile range. Categorical variables are described as frequency and percentage. Comparison groups were made using the t test for parametric distribution variables and the Mann-Whitney test for non-parametric distribution variables. Variables that showed a possible association with the outcome of death ($p < 0.1$) or with biological plausibility were included in the multivariate model through binary logistic regression. The probability value <0.05 was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) version 20.0 was used for data analysis.

This research was registered and followed the necessary procedures; the project was approved by the local ethics committee under the registration number CAAE 39774620.4.0000.0045.

RESULTS

Were evaluated 194 patients, but 41 were excluded for having non-rheumatic etiology for mitral dysfunction, 2 for having associated interatrial septal defect, 5 for having primary rheumatic tricuspid valve disease and 2 for active endocarditis; 144 patients were included.

The mean age was 46.2 (±12.3) years with 107 (74.3%) female individuals, the median left ventricular ejection fraction was 61.0% (55 - 67) and sPAP was 55.0 mmHg (46 - 74), with 45 (31.3%) individuals with right ventricular dysfunction. The predominant valve disease was mitral stenosis (74.3%). The prevalence of severe tricuspid regurgitation was 47.2%. Tricuspid annuloplasty was performed in 83 (57.6%) patients. The median time of cardiopulmonary bypass (CPB) 90min (68 - 125). The frequency of concomitant aortic valve replacement: 53 (36,8%). The total in-hospital mortality was 15 (10.4%) individuals.

In the univariate analysis, sPAP was associate with early surgical death 1.04 (1.01 – 1.06) p=0.002. In the multivariate analysis, involving four variables with a potential prediction of death in 30 days, there was an association with only one variable independently: the sPAP value, RR 1.04 (1.01 – 1.07), p = 0.003. To determine a sPAP cut-off that indicates higher mortality and help decision making in clinical practice, we performed an analysis through the ROC curve (area 0.70, p=0.012). The estimated value of 73.5mmHg has the highest accuracy in our model for predicting early mortality (Figure 1).

DISCUSSION

In this study evolving rheumatic mitral valve disease individuals undergoing cardiac surgery, we found that pulmonary hypertension is associate with early surgical mortality. At our model, values of sPAP above 73.5mmHg predicts a higher risk.

The association between pulmonary hypertension and surgical death is already describe at literature, however, a cutoff point of sPAP that discriminate individuals of higher and lower risk it's not well established. Mubeen and colegues reported that mitral valve replacement can be safely performed in patients with moderate to severe PH with an operative mortality of 5.5%. By contrast, they found an operative mortality of 28.5% in patients with supra systemic PH and high pulmonary vascular resistance.

The mortality observed in our study is similar to that found in the study by Kuwaki et al (14) with in-hospital mortality of 8.9% of surgeries for correction of left valve disease associated with significant tricuspid insufficiency in a Japanese center, as well as mortality of cardiac surgery in centers in developing countries such as the surgical mortality of 8.9% described in the study by Mejia et al (15) for cardiac surgery performed at a specialized center in Brazil attended by the public health system with restricted access to procedures of high complexity, in which many individuals are diagnosed and treated late in the natural history of the disease.

After multivariate analysis, the value of sPAP, was identified as predictor of higher hospital mortality. Individuals with greater severity of pulmonary hypertension are more likely to develop acute right ventricular dysfunction and circulatory shock in the immediate postoperative period (17,18). Therefore, the severity of pulmonary hypertension should be considered in the discussions of Heart Team when dealing with patients with a natural history of advanced disease and high surgical risk in weighting risks versus benefit of left valve surgery.

The study has limitations, it’s a single-center cohort, being subject to the biases inherent to this model, but maintains its clinical relevance because the population studied is composed exclusively of patients with rheumatic mitral valve disease, reducing the heterogeneity, since there is a paucity of trials contemplating exclusively this population in this scenario.

CONCLUSION

In patients with rheumatic heart disease who will undergo mitral valve surgery, pulmonary hypertension is associated with higher early mortality. Values above 73.5 mmHg predict higher risk and, in this part of the population, additional measures to control intraoperative and immediate postoperative pulmonary hypertension should be considered.

FUNDING STATEMENT

None.

CONFLICT OF INTEREST STATEMENT

None.

AUTHOR CONTRIBUTION STATEMENT

Gustavo P Santana: Conceptualization, Methodology, Formal analysis, Writing - Original Draft

Rodrigo M Vieira de Melo: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Project administration

Tainá T Viana: Conceptualization, Writing - Review & Editing

Luanna M Damasceno: Data Curation

Pedro F Soares: Data Curation

José VS Santos: Data Curation

Arthur Tolentino: Data Curation

Edmundo JN Câmara: Conceptualization, Methodology, Formal analysis,

Luiz CS Passos: Supervision, Conceptualization, Methodology

TABLES

Table 1 - Demographic and baseline clinical characteristics

	Total (n = 144)	**Tricuspid repair (n = 83)**	**No tricuspid repair (n = 61)**	**P[a]**
Age, mean (±SD)	46.2 (±12.3)	46.3 (±12.8)	46.0 (±11.5)	0.786
Female sex, n (%)	107 (74.3%)	65 (78.3%)	42 (68.9%)	0.199
Mitral stenosis moderate or severe, n (%)	107 (74.3%)	62 (74.7%)	45 (73.8%)	0.999
Mitral regurgitation moderate or severe, n (%)	83 (57.6%)	47 (56.6%)	36 (59.0%)	0.999
Severe tricuspid regurgitation, n (%)	83 (57.6%)	54 (65.1%)	29 (47.5%)	0.001
NYHA III ou IV, n (%)	54 (37.5%)	32 (38,5%)	22 (36.0%)	0.865
Atrial fibrillation, n (%)	94 (65.3%)	56 (67.5%)	38 (62.3%)	0.519
LVEF, median (IQ)	61.0 (55.0 – 67.0)	62.0 (54.5 – 67.0)	60,00 (55.0 – 68.0)	0.886
sPAP, median (IQ)	55.0 (46.0 – 74.0)	57.0 (47.0 – 75.0)	51.00 (43.3 – 69.8)	0.124
Dysfunction of right ventricle, n (%)	45 (31.3%)	27 (32.5%)	18 (29.5%)	0.531

LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure

[a] p value: comparison between tricuspid repair group and no tricuspid repair.

Table 2 - Surgical characteristics of individuals

	Total (n = 144)	**Tricuspid repair (n = 83)**	**No tricuspid repair (n = 61)**	**P[a]**
Aortic valve replacement, n (%)	53 (36.8%)	26 (31.3%)	27 (44.3%)	0.112
Myocardial revascularization, n (%)	6 (4.2%)	4 (4.8%)	2 (3.3%)	0.999
Reoperation, n (%)	25 (17.4%)	15 (18.1%)	11 (18.0%)	0.999
Mechanical prosthesis, n (%)	112 (77.8%)	64 (77.1%)	48 (78.7%)	0.822
CPB time, min (IQ)	90 (68 – 125)	99 (75 – 140)	85 (61 – 118)	0.038
Aortic cross clamp, min (IQ)	80 (55 – 115)	80 (62 – 115)	75 (51 – 105)	0.082

CPB: cardiopulmonary bypass

[a] p value: comparison between tricuspid repair group and no tricuspid repair.

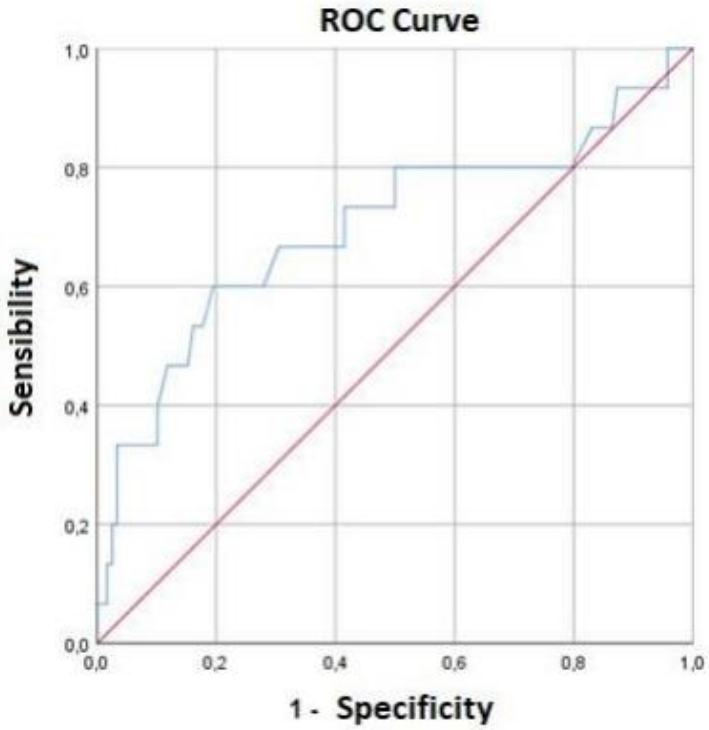
Table 3: Univariate and multivariate analysis for surgical death

	Univariate analysis RR (95% CI)	**P**	**Multivariate analysis** RR (95% CI)	**P**
Age	1.01 (0.97 – 1.06)	0.599	1.02 (0.77 – 1.07)	0.319
sPAP	1.04 (1.01 – 1.06)	0.002	1.04 (1.01 – 1.07)	0.003
Tricuspid repair	1.53 (0.50 – 4.74)	0.457	1.06 (0.29 – 3.89)	0.936
Severe TR	3.47 (1.05 – 11.49)	0.041	3.28 (0.87 – 12.30)	0.078
NYHA III-IV	0.70 (0.22 – 2.23)	0.550		
Right ventricle dysfunction	1.62 (0.53 – 4.97)	0.403		
CPB time	1.01 (1.01 – 1.02)	0.001		
Aortic cross clamp time	1.01 (1.01 – 1.03)	0.003		
LVEF	1.04 (0.99 – 1.10)	0.109		

LVEF: left ventricle ejection fraction; NYHA: New York Heart Association; sPAP: systolic pulmonary artery pressure; TR: tricuspid regurgitation

FIGURES

Figure 1 – ROC Curve (area 0.70, p=0.012)



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