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BMJ Open

Value of pulmonary artery pressure in predicting in-hospital and one-year mortality after valve replacement surgery in middle-aged and aged patients with rheumatic mitral disease: an observational study

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ABSTRACT

Objectives To investigate the role of pulmonary artery pressure (PAP) in predicting in-hospital death after valve replacement surgery in middle-aged and aged patients with rheumatic mitral disease.

Design An observational study.

Setting Guangdong General Hospital, China.

Participants 1639middle-aged and aged patients (mean age 57±6 years) diagnosed with rheumatic mitral disease, undergoing valve replacement surgery and receiving coronary angiography and transthoracic echocardiography before operation, were enrolled.

Interventions All participants underwent valve replacement surgery and received coronary angiography before operation.

Primary and secondary outcome measures In-hospital death and 1-year mortality after operation.

Methods Included patients were divided into four groups based on the preoperative PAP obtained by echocardiography: group A (PAP≤30 mm Hg); group B (>30 mm Hg<PAP≤50 mm Hg), group C (>50 mm Hg<PAP≤70 mm Hg) and group D (PAP>70 mm Hg). The relationship between PAP and in-hospital death and cumulative rate of 1-year mortality was evaluated.

Results In-hospital mortality rate increased gradually but significantly as the PAP level increased, with 1.9% in group A (n=268), 2.3% in group B (n=771), 4.7% in group C (n=384) and 10.2% in group D (n=216) (p<0.001). Multivariate analysis showed that PAP>70 mm Hg was an independent predictor of in-hospital death (OR=2.93, 95% CI 1.61 to 5.32, p<0.001). PAP>52.5 mm Hg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (area under the curve=0.672, 95% CI 0.602 to 0.743, p<0.001). Kaplan–Meier analysis showed that patients with PAP>52.5 mm Hg had higher 1-year mortality after operation than those without (log-rank=21.51, p<0.001).

Conclusions PAP could serve as a predictor of postoperative in-hospital and 1-year mortality after valve replacement surgery in middle-aged and aged patients with rheumatic mitral disease.

Strengths and limitations of this study

- 3.8% of middle-aged and aged patients receiving mitral valve replacement died during or shortly after surgery.
- Pulmonary artery pressure (PAP) could serve as a predictor of postoperative in-hospital mortality after valve replacement surgery in middle-aged and aged patients with rheumatic mitral disease.
- PAP>52.5 mm Hg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death.
- PAP>52.5 mm Hg had higher 1-year mortality after operation than those without.
- Since the reproducibility and reliability of echocardiography in calculating PAP are lower than with right heart catheterisation, clear correlation between PAP level and post-surgery mortality was unknown.

INTRODUCTION

Rheumatic heart disease (RHD) caused by rheumatic fever is uncommon in developed countries, but remains a major health problem in developing countries.[1–3]

Approximately 50% of RHD affects the mitral valve, resulting in mitral stenosis, mitral regurgitation, or both.[4] Valve replacement surgery is an important treatment for rheumatic mitral disease.[5] However, according to the meta-analysis conducted by Guida *et al*[6] 2.95% (4293/145 592) of patients undergoing cardiac surgery including valve replacement had postoperative mortality. Therefore, identifying the high risk factor(s) for poor outcomes remains urgent and important.

Pulmonary hypertension (PH) is a common complication of rheumatic mitral disease,

which is correlated with poor outcome in patients undergoing heart surgery, particularly in middle-aged and aged patients.[7] Pulmonary artery pressure (PAP) can be easily measured using Doppler echocardiography, which is considered the best screening method for PH.[8] However, whether the PAP could serve as a suitable predictor of poor outcome, particularly high mortality, in patients with rheumatic mitral disease is not clear and the cut-off value for PAP as a predictor has not been defined. This study aimed to determine whether PAP measured by echocardiography could be a valuable parameter in predicting in-hospital death or the cumulative rate of 1-year mortality after surgery in middle-aged and aged patients with rheumatic mitral disease.

PATIENTS AND METHODS

Patients

In this study, we enrolled middle-aged and aged patients with a diagnosis of rheumatic mitral disease from Guangdong General Hospital, Guangzhou, China between March 2009 and July 2013. RHD was diagnosed according to previous acute rheumatic fever and/or symptoms of precordial abnormalities, the presence of a heart murmur and valve abnormality on echocardiography.[9] All patients received mitral valve replacement surgery in this study. PAP levels were measured using transthoracic echocardiography, and coronary angiography was performed to exclude coronary heart disease in all patients. The exclusion criteria were (i) patients with known primary PH or pericardial disease, (ii) patients presenting with pulmonary vessel disease and chronic obstructive pulmonary disease, (iii) patients with previous valve replacement surgery and (iv) patients who did not have an echocardiographic examination before surgery.

The patients (n=1639) were divided into four groups based on the preoperative PAP on echocardiography: PAP≤30 mm Hg in group A (n=268); >30 mm Hg<PAP≤50 mm Hg in group B (n=771); >50 mm Hg<PAP≤70 mm Hg in group C (n=384) and PAP>70 mm Hg in group D (n=216). The cut-off values were decided according to clinical guidelines.[5 6] This study was approved by the ethics committee of the hospital (GDREC2014016H R1) and written informed consent was obtained from all enrolled participants.

Echocardiography

M-mode, two-dimensional and Doppler tissue imaging were performed according to guidelines of the American Society of Echocardiography[10] before valve replacement surgery. Left ventricular end-diastolic and right ventricular diameters were obtained in the parasternal long-axis view using M-mode images. Left ventricular ejection fraction (LVEF) was evaluated using the biplane Simpson's method. Mitral and tricuspid regurgitation were measured based on the jet area within the left or right atrium, respectively. PAP was estimated by Doppler echocardiography by calculating the right ventricular to right atrial pressure gradient during systole, approximated by the modified Bernoulli equation as $4v^2$, where v is the velocity of the tricuspid regurgitation jet in m/s.[11] Although the agreement between echocardiographic estimates of PAP and invasively measured values on right heart catheterisation is suboptimal,[12] especially among patients with lung disease,[13] echocardiography is a more convenient and practical approach than right heart catheterisation. On the other hand, both echocardiography and right heart catheterisation have been reported to be suitable for PH screening.[14]

Definitions and endpoints

Coronary artery disease was defined as main coronary stenosis ≥50 according to coronary angiography. The primary endpoint of this study was death from any cause except suicide during hospitalisation. One-year mortality after operation was considered as secondary endpoint.

Statistical analysis

Continuous variables were described as mean±SD and difference among groups was compared by analysis of variance (ANOVA) and post hoc analysis was further performed to detect the difference between two particular groups. Abnormally distributed data were shown as median (first and third quartiles) and the difference was analysed by non-parametric Mann–Whitney U test. Categorical variables were shown as numbers (percentages), and the comparison of the groups was done by χ^2 test. Multiple logistic regression analysis was performed to discover the risk factors. Receiver operating characteristic curves were presented to evaluate the predictive value of PAP for in-hospital death. All the statistical analyses were carried out using SPSS 11.0 software program and $p<0.05$ was considered statistically significant.

RESULTS

Baseline clinical characteristics of the cohort

A total of 1749 middle-aged and aged patients with rheumatic mitral valve disease undergoing valve replacement surgery were originally enrolled in this study, of whom 19 had a past medical history of valve replacement surgery. Preoperative echocardiography data were missing in 90 patients and one patient committed suicide during hospitalisation, resulting in a final number of 1639 patients being recruited to this study. Five hundred and twelve subjects were male and 1127 were female with an average age of 57±6 years.

Other clinical characteristics of this population are summarised in table 1. In brief, patients in other groups had higher incidence of atrial fibrillation than patients in group A ($p=0.006$, χ^2 test), possibly owing to their high PAP and potentially changed left atrium structure. There were significant differences in the proportion of patients with New York Heart Association (NYHA) >II and in the right ventricle (RV) diameter among the four groups, with patients in group D, who had the highest PAP, having the greatest percentage of subjects with NYHA>II and largest RV

Table 1 Clinical characteristics of the patients

Clinical variables	Group A (n=268)	Group B (n=771)	Group C (n=384)	Group D (n=216)	p Value
Age (years)	57.5±5.4	57.6±5.5	57.5±5.6	57.0±6.2	0.594
Female subjects, n (%)	174 (64.9)	532 (69.0)	280 (72.9)	141 (65.3)	0.104
Smoking, n (%)	38 (14.2)	82 (10.6)	38 (9.9)	21 (9.7)	0.293
Hypertension, n (%)	33 (12.3)	97 (12.6)	39 (10.2)	23 (10.6)	0.617
Diabetes mellitus, n (%)	14 (5.2)	43 (5.6)	24 (6.3)	20 (9.3)	0.217
Coronary artery disease, n (%)	18 (6.7)	45 (5.8)	16 (4.2)	10 (4.6)	0.462
Atrial fibrillation, n (%)	146 (54.5)	504 (65.4)	252 (65.6)	128 (59.3)	0.006
NYHA>II, n (%)	109 (40.7)	316 (41.0)	189 (49.2)	125 (57.9)	<0.001
eGFR (mL/min/1.73 m^2)	89.6±26.4	88.0±24.3	88.0±26.1	84.2±24.5	0.116
Haemoglobin (g/L)	137.5±14.0	135.4±15.9	131.3±16.8	130.6±15.8	<0.001
LVEF, %	61.7±9.7	62.1±8.4	60.1±9.6	62.1±10.2	0.004
RV diameter, mm	48.9±7.7	50.2±6.8	53.7±7.6	55.5±9.0	<0.001
LVEDD index, mm/m^2	50.5±9.8	49.0±7.9	49.0±8.6	45.4±9.2	<0.001
MR volume, cm^2					
<4	107 (39.9)	278 (36.1)	147 (38.3)	104 (48.1)	0.003
4–8	73 (27.2)	208 (27.0)	82 (21.4)	35 (16.2)	
>8	88 (32.8)	285 (37.0)	155 (40.4)	77 (35.6)	
MVA≤1.5 cm^2	228 (85.1)	670 (86.9)	323 (84.1)	194 (89.8)	0.222
TR volume, cm^2	1.9 (0, 3.2)	4.8 (2.8, 7.4)	8.3 (5.3, 11.4)	10.4 (6.9, 14.3)	<0.001
Aortic valve replacement	107 (39.9)	302 (39.2)	152 (39.6)	83 (38.4)	0.988
CABG	17 (6.3)	35 (4.5)	14 (3.6)	10 (4.6)	0.452
In-hospital death	5 (1.9)	18 (2.3)	18 (4.7)	22 (10.2)	<0.001

CABG, coronary artery bypass grafting.; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVA, mitral valve area; NYHA, New York Heart Association; RV, right ventricle; TR, tricuspid regurgitation.

diameter (table 1). Lower haemoglobin was found in groups C and D compared with group A (ANOVA p<0.001, and post hoc test p<0.05 vs group A). In addition, a lower left ventricular end-diastolic diameter index and mitral regurgitation volume were present in group D (ANOVA p<0.001, and post hoc test p<0.05 vs group A). Additionally, patients in group C had a significantly lower LVEF than those in group A (p<0.05). Increasing PAP level was associated with higher tricuspid regurgitation volume (ANOVA p<0.001). Sixty-three patients died during hospitalisation with 5 (1.9%) in group A, 18 (2.3%) in group B, 18 (4.7%) in group C and 22 (10.2%) in group D (p<0.001, χ^2 test). No significant differences in the clinical data were seen among the groups.

Of these 1639 patients, 1459 subjects (89.0%) completed the 1-year follow-up after operation, during which time 75 patients died, including 7 (3.0%) in group A, 23 (3.3%) in group B, 20 (5.9%) in group C and 25 (13.2%) in group D (p<0.001).

Correlation analysis between PAP levels and other parameters

Among all patients, PAP levels had a positive correlation with RV diameter (r=0.270, p<0.001) and tricuspid regurgitation volume (r=0.507, p<0.001), and negative correlation with estimated glomerular filtration rate (r=−0.074 p=0.003), left ventricular end-diastolic diameter index (r=−0.204, p<0.001) and haemoglobin concentrations (r=−0.141, p<0.001).

Role of PAP for in-hospital mortality

Univariate analyses for mortality showed that age, diabetes mellitus, anaemia, lower estimated glomerular filtration rate, LVEF <50%, larger RV diameter, tricuspid regurgitation volume, previously received coronary artery bypass grafting (CABG) and higher PAP were associated with increased in-hospital mortality (table 2). These variables were included in a multiple logistic regression analysis for adjustment of potential biased factors. We found that PAP>70 mm Hg (OR=2.93, 95% CI 1.61 to 5.32, p<0.001) remained an independent predictor of in-hospital death, after adjusting for age, diabetes mellitus and previously received CABG. Of note, age (OR=1.07, 95% CI 1.02 to 1.12, p=0.006), diabetes mellitus (OR=2.50, 95% CI 1.16 to 5.38, p=0.019), LVEF <50% (OR=2.09, 95% CI 1.05 to 4.15, p=0.036), tricuspid regurgitation volume (OR=1.05, 95% CI 1.01 to 1.09, p=0.021) and received CABG (OR=2.96, 95% CI 1.26 to 6.93, p=0.012) were also independent risk factors for in-hospital death (table 2).

Table 2 Univariate analysis and multiple logistic regression analysis for in-hospital death.

	Univariate analysis		Multiple logistic regression		
Clinical variables	**OR**	**p**	**OR**	**95% CI**	**p Value**
Age (years)	1.09	<0.001	1.07	1.02 to 1.12	0.006
Female subjects	0.73	0.233			
Smoking	1.02	0.961			
Hypertension	1.27	0.518			
Diabetes mellitus	3.08	0.002	2.50	1.16 to 5.38	0.019
Coronary artery disease	1.53	0.374			
Atrial fibrillation	0.84	0.491			
NYHA>II	1.66	0.052			
Anaemia	2.90	0.001	1.89	0.93 to 3.85	0.080
eGFR<60 mL/min/1.73 m^2	2.57	0.003	1.64	0.82 to 3.27	0.159
MVA≤1.5 cm^2	0.83	0.604			
LVEF<50%	2.40	0.007	2.09	1.05 to 4.15	0.036
RV diameter	1.05	0.002	1.02	0.98 to 1.05	0.411
LVEDD index	1.02	0.196			
MR>8 cm^2	1.05	0.843			
TR volume	1.07	<0.001	1.05	1.01 to 1.09	0.021
Aortic valve replacement	1.52	0.100			
CABG	3.23	0.003	2.96	1.26 to 6.93	0.012
PAP>70 mm Hg	3.82	<0.001	2.93	1.61 to 5.32	<0.001

CABG, coronary artery bypass grafting.; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PAP, pulmonary artery pressure; RV, right ventricle; TR, tricuspid regurgitation.

In addition, we obtained a receiver operating characteristic curve to determine the predictive value of PAP for in-hospital death in patients with rheumatic mitral valve disease after valve replacement surgery. PAP>52.5 mmHg had a sensitivity of 60.3% and specificity of 67.7% in predicting in-hospital death (area under the curve = 0.672, 95% CI 0.602 to 0.743, p<0.001, figure 1). Kaplan–Meier analysis showed that patients with PAP>52.5 mmHg had a higher 1-year mortality than those without (log-rank=21.51, p<0.001) (figure 2).

DISCUSSION

This study found that PAP assessed by echocardiography can be a useful predictor for in-hospital death and 1-year mortality after valve replacement surgery in patients with rheumatic mitral disease. In addition, 3.8% of middle-aged and aged patients receiving mitral valve replacement died during or shortly after surgery, which was in accordance with previous research. Furthermore, the cut-off value of PAP>52.5 mm Hg can be used for risk assessment in middle-aged and aged patients with rheumatic mitral disease.

In addition to left to right bypass in congenital heart disease, RHD is another major cause of PH due to the increased cardiac preload and passive chronic reconstruction of pulmonary vessels.[15] This chronic vessel remodelling could result in increased media thickness, intimal hyperplasia, fibrosis and ultimately, narrowing of pulmonary vessels.[16] There is no well-defined

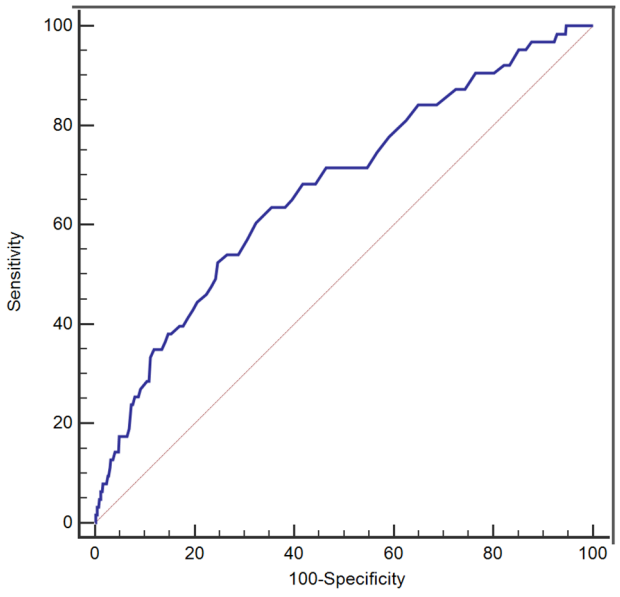

Figure 1 Receiver operating characteristic curve of all patients in this study.

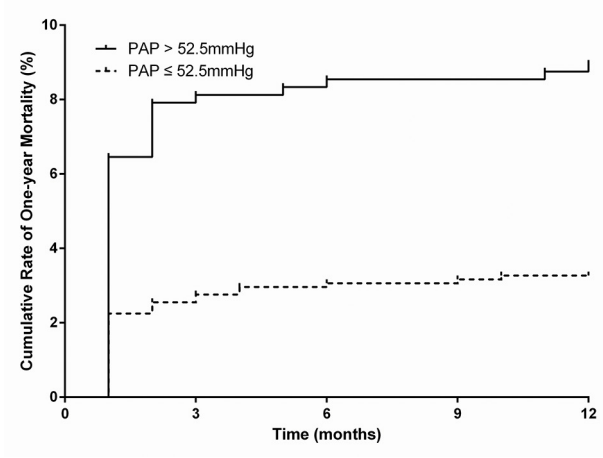

Figure 2 Kaplan–Meier survival curve of different groups. PAP, pulmonary artery pressure.

and recognised classification of pulmonary vascular pathology secondary to rheumatic heart disease. Mubeen *et al* enrolled 24 patients in a previous study who were diagnosed with RHD and PH. The inferior lobe of right lung tissues was obtained during surgery and the authors reported that the pathological changes of patients with PH and RHD are reversible.[17] Nevertheless, the study carried out by Tandon *et al* in about 100 patients with both RHD and PH showed pathological change such as telangiectasis, fibrous tissue proliferation and thickening, vessel stenosis and occlusion under the microscopy. More importantly, the authors claimed that such pathological changes can not be reversible.[18] These conflicting results indicate that the degree of pathological changes and reconstruction of pulmonary vessels is closely related to the severity of PH.

RHD combined with PH induces pathological changes of pulmonary vessels, since the progression of PH usually leads to increased right cardiac afterload and subsequently, right ventricular hypertrophy and heart failure. In our study, we found that both RV diameter and NYHA grade were significantly different among the four groups of PAP levels, with patients with the highest PAP levels having the biggest RV diameter and highest percentage with NYHA>II, suggesting that a RV structure change has happened at a stage of severe PH. Moreover, severe pulmonary venous pleonaemia could lead to anoxia and carbon dioxide retention, which might further increase heart damage, accounting for continuous deteriorating heart function.[19] A previous study proved that right ventricular dysfunction was associated with poor outcomes.[20]

Although the stress on the pulmonary artery and resistance of pulmonary vessels could be greatly reduced after rheumatic mitral regurgitation surgery, the pulmonary pressure of patients with RHD combined with severe PH does not usually return to a normal level. Owing to the severe pulmonary vascular wall remodelling, the morphological change of the pulmonary vessel wall is irreversible at a later stage when patients are receiving surgery. Thus the pulmonary artery stress could persist and exceed the systemic arterial blood pressure before the operation. In this case the right cardiac afterload would be further aggravated after the operation, which might lead to low cardiac output syndrome.[21 22] Therefore, postoperative mortality was still high in patients with higher PAP.

Pulmonary venous pleonaemia, pulmonary vascular remodelling and a decrease of lung compliance may increase the difficulties of patients with rheumatic mitral regurgitation combined with severe PH, leading to serious complications, including respiratory failure. In addition, as the severity of PH increases and vascular remodelling occurs, factors such as acute lung injury, anoxia or sympathetic stage in cardiopulmonary bypass in the operation may also increase the possibility of complications, especially a pulmonary hypertensive crisis, which carries mortality of >40%.[23] The findings of our study prove that the greater the severity of the preoperative PAP level , the higher the in-hospital mortality and 1-year follow-up mortality in patients with rheumatic mitral disease.

The significance of this study lies in the fact that we have a 1-year follow-up dataset. These data indicate that severe PH may be a powerful predictor of the outcome of in-hospital death and 1-year mortality after valve replacement surgery. To the best of our knowledge, this is the first study designed to focus on the value of PAP in deciding the prognosis of middle-aged and aged patients with rheumatic mitral disease. PAP>52.5 mm Hg had a sensitivity of 60.3% and specificity of 67.7% for predicting in-hospital death which was a good preliminary result from a single-centre study. Moreover, PH might be a potential therapeutic target in valve replacement surgery of RHD. A future randomised trial is warranted to confirm whether decreasing PAP by drug treatment,[24 25] below the cut-off point indicated in our study, would lead to a better outcome.

This study had some limitations. First, as this was a retrospective analysis based on prospectively collected data, some confounding might have affected the results. To overcome this inherent weakness, multivariate logistic regression was performed. Second, PAP was not measured by right heart catheterisation, the 'gold standard', which is more reliable than echocardiography.[14] Even so, echocardiography is a more convenient and practical approach than right heart catheterisation. Third, whether postoperative PAP affected the prognosis was unclear because PAP could not be accurately measured by echocardiography in patients with tricuspid valve repair.

CONCLUSION

In conclusion, we found that PAP could serve as a predictor of postoperative in-hospital and 1-year mortality after valve replacement surgery in middle-aged and aged patients with rheumatic mitral disease.

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Contributors D-QY and NT contributed to the conception or design. LJ, X-BW, P-CH, DF, Y-HL and J-YL contributed to the collection and assembly of the data. X-BW and P-CH contributed to data analysis and interpretation. LJ and X-BW contributed to writing of the manuscript . D-QY, NT and J-YC critically revised the manuscript. All authors were involved in final approval of the version to be published.

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Ethics approval Guangdong General Hospital.

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