Original Article

Pulmonary Hypertension in Mitral Valve Disease-Rheumatic Mitral Stenosis versus Organic Mitral Regurgitation: The Doppler-Echocardiographic Study Revisited

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Background: Pulmonary hypertension (PH) is common in patients with mitral valve disease.

Objective: To determine the factors associated with PH among patients with mitral valve disease, and the similarities and differences in the subgroups of mitral stenosis (MS) and mitral regurgitation (MR).

Materials and Methods: Patients with isolated moderate to severe organic mitral valve disease were prospectively enrolled. PH was defined echocardiographically as pulmonary artery systolic pressure of more than 50 mmHg. Patients with MS who had mitral valve area of more than 1.5 cm^2 and patients with MR who had effective regurgitant orifice area of less than 20 mm^2 were excluded.

Results: Three hundred eighteen patients with a mean age of 54.3±15.5 years including 57.6% female and 66.7% MR were included in this study. PH was present in 119 patients (37.4%), including 48.1% in MS and 31.8% in MR. Severe mitral valve disease was reported in 245 patients (77.0%). Left atrial (LA) diameter and pulmonary artery pressure were significantly higher in patients with MS. Dyspnea, LA volume index, significant tricuspid and pulmonary regurgitation, severe mitral valve disease, and the presence of MS were independently associated with PH. Among patients with MS, LA volume index and severe disease were independently associated with PH. Significant tricuspid and pulmonary regurgitation, LA volume index and severe disease were independently associated with PH in patients with MR.

Conclusion: PH is common in patients with mitral valve disease. LA volume index and severe disease were, in common, independently associated with PH in patients with mitral valve disease and in the subgroups of MS and MR.

Keywords: Mitral regurgitation; Mitral stenosis; Pulmonary hypertension; Rheumatic heart disease

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Mitral valve disease is common and can be classified according to the anatomical and pathophysiological abnormalities into mitral stenosis (MS) and mitral regurgitation (MR). Pulmonary hypertension (PH) is a common consequence of mitral valve disease and has been reported to occur in 23% to 33% of patients[1-4]. Chronic pressure and volume overload of the left atrial (LA) in patients with mitral valve disease leads to an increased LA pressure, LA enlargement, and subsequently, a passive backward transmission of pressure to the pulmonary vascular bed, which triggers pulmonary vasoconstriction, leading to PH[5]. LA remodeling, atrial fibrillation, and PH share in common the ultimate pathophysiological consequences and are of prognostic significance in patients with MS and MR. The presence of PH, defined as pulmonary artery systolic pressure of 50 mmHg or greater at rest, is a valuable sign in determining the need for valvular intervention in patients with mitral valve disease[6,7]. Previous studies have verified the factors associated with PH such as age, LA enlargement, and MR severity, in patients with isolated organic MR[1-3]. However, this issue remains under-recognized in patients with MS. The objectives of the present study were to determine the factors associated with PH in

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patients with mitral valve disease and, specifically, in the subgroups of patients with MS and MR. The present study also evaluated the similarities and differences regarding the echocardiographic findings in patients with MS versus MR.

Materials and Methods

Patient selection

The study population consisted of consecutive patients over 18 years of age who had clinical indications that warranted echocardiography. Patients with a diagnosis of isolated moderate to severe organic mitral valve disease were prospectively enrolled in the present study. Patients with mild MS, defined as a mitral valve area of greater than 1.5 cm^2 and patients with mild MR, defined as an effective regurgitant orifice area smaller than 20 mm^2, were excluded. Other exclusion criteria were patients with combined significant MS and MR, functional MR, previous percutaneous balloon mitral valvotomy, co-existing moderate to severe aortic valve disease, a prosthetic valve, previous cardiac surgery, left ventricular systolic dysfunction such as left ventricular ejection fraction or less than 50%, congenital or pericardial disease, renal dysfunction, human immunodeficiency virus infection, thalassemia, thyroid disease, pulmonary or hepatic disease, and those who had a limited or poor-quality echocardiographic study.

Vital signs and an electrocardiogram were obtained in all patients on the day of echocardiography. Dyspnea was defined using the New York Heart Association function classes II-IV. The study protocol was approved by the Institutional Review Board of Siriraj Hospital, Mahidol University, Bangkok, Thailand (certificate of approval no. 626/2011). Informed consent was obtained from all patients.

Echocardiography

All patients underwent a comprehensive transthoracic echocardiographic examination, including 2-dimensional and 3-dimensional, M-mode, Doppler echocardiography, and tissue Doppler imaging. The average of three to five consecutive cardiac cycles was used for the analysis of echocardiographic measurements. The severity of MR was quantitatively assessed using proximal isovelocity surface area method and grading according to standard recommendations[8]. The severity of MS was graded using mitral valve area by two-dimensional echocardiography[9]. The mitral valve anatomy in MS was assessed using Wilkins score[10]. Patients with MS found to have a mitral valve area of less than 1.0 cm^2[9], and patients with MR found to have an effective regurgitant orifice area of 40 mm^2 or more and regurgitant volume of 60 mL or more were considered to have severe disease. Continuous-wave and pulse-wave Doppler spectra of pulmonic regurgitation and tricuspid regurgitation were obtained for the determination of pulmonary artery pressure, including mean pulmonary artery pressure, pulmonary artery end-diastolic pressure, pulmonary vascular resistance, and pulmonary artery systolic pressure[11]. PH was defined as pulmonary artery systolic pressure of more than 50 mmHg[6,7]. The severity of pulmonic regurgitation and tricuspid regurgitation were determined using the combination of multiple parameters[8]. Moderate or greater degree of pulmonic regurgitation and tricuspid regurgitation were considered significant regurgitation. LA diameter, LA volume, left ventricular dimensions, volume, mass, and systolic function were evaluated as previously recommended[12] and indexed for body surface area. The assessment of right ventricular systolic function was performed using the tricuspid annular plane systolic excursion and the peak systolic myocardial velocity of lateral tricuspid annulus[12].

Statistical analysis

Subject characteristics were reported using descriptive statistics, including frequencies and percentage for categorical variables. Continuous variables were reported as mean ± standard deviation for normally distributed variables and median (25^{th} to 75^{th} percentile) for non-normally distributed continuous variables. Normality of distribution of variables was examined by Kolmogorov-Smirnov test. The student t-test and Mann Whitney test were used to compare continuous variables, whereas chi square and Fisher's exact test were performed for categorical variables. Univariate and multivariate factors associated with PH were evaluated using logistic regression analysis (forward stepwise method for multivariate analysis) and presented as an odds ratio (95% confidence interval). The interclass correlation coefficient was performed to determine the intra- and inter-observer variability for the estimation of pulmonary artery systolic pressure and the results were 0.991 (0.981 to 0.996) and 0.995 (0.989 to 0.998), respectively. For all tests performed, a two-tailed p-value less than 0.05 was considered to be statistically significant. PASW Statistics, version 18.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

Three hundred eighteen patients were enrolled in the present study. Their mean age was 54.3±15.5 years of whom 183 (57.6%) were female. PH was reported in 119 patients (37.4%). Table 1 shows the baseline characteristics and echocardiographic data in all patients and in patients with and without PH. Dyspnea, history of heart failure, atrial fibrillation, the use of diuretics and anticoagulants, and severe mitral valve disease were significantly more common in patients with PH.

Patients with MS and MR accounted for 33.3% and 66.7% of patients, respectively. PH was reported in 48.1% of the patients with MS and 32.1% of the patients with MR. All cases of MS were rheumatic in origin. Among patients with MR, ruptured chordae and flail mitral valve leaflets were the most common etiologies in 44.8%. Mitral valve prolapse without ruptured chordae or flail leaflets, and isolated rheumatic MR were reported in 35.8% and 11.7% of patients with MR, respectively. Baseline characteristics, electrocardiographic, and echocardiographic findings in patients with MS and MR are shown in Table 2. Dyspnea, history of stroke and atrial fibrillation were more common in patients with MS than those with MR. Table 3 shows the comparisons of baseline characteristics and echocardiographic data in patients with and without PH as well as the subgroups of patients with MS and MR.

An electrocardiogram on the day of the study revealed atrial fibrillation in 67.0% of the patients with MS and 31.3% of the patients with MR ($p<0.001$). Right and left axis deviation were reported in 8.9% and 5.7% of patients, respectively. LA enlargement and left ventricular hypertrophy were observed in 28.4% and 31.9% of patients, respectively. Atrial fibrillation was significantly more common in patients with PH than those without at 56.3% versus 35.4% ($p<0.001$), and in patients with MS than those with MR at 67.0% versus 37.3% ($p<0.001$).

In univariate analysis, dyspnea, atrial fibrillation, left ventricular ejection fraction, LA volume index, significant tricuspid regurgitation, significant pulmonic regurgitation, tricuspid annular plane systolic excursion, and clinically more severe disease were significantly associated with PH in patients with mitral valve disease. This was also true for patients with MS as in patients with MR. Table 4 shows independent factors associated with PH in patients with mitral valve disease and in the subgroups of MS and MR.

Discussion

PH is common in patients with mitral valve disease. The present study demonstrated that 37.4% of patients with moderate to severe mitral valve disease had PH, while an incidence of 23% to 33% was reported in previous studies[1-4]. LA volume index and a severe disease are both independent determinants of PH in patients with mitral valve disease and in the subgroups of MS and MR. Furthermore, the present study demonstrated the importance of significant right-sided valvular regurgitation as an independent determinant of PH in patients with mitral valve disease and the subgroup of MR.

The presence of PH in patients with mitral valve disease adversely affects the clinical symptoms and it is a predictor of poor long-term outcome, including event-free survival, even after successful corrective interventions[13,14]. Patients with mitral valve disease and PH are vulnerable to right heart failure or pulmonary edema, which contribute to the morbidity and mortality. The current guidelines on treatments of valvular heart disease recommend valvular intervention for asymptomatic patients with mitral valve disease and pulmonary artery systolic pressure greater than 50 mmHg[6,7].

The initial insult leading to PH in chronic mitral valve disease differs between MS and MR. MS leads to LA pressure overload imposed by the stenotic mitral valve, while MR leads to volume overload from significant regurgitation. Despite these different pathophysiological mechanisms, the common anatomical and physiologic changes include an increased LA pressure, LA enlargement, a passive backward transmission of pressure to the pulmonary vessels, pulmonary vasoconstriction, irreversible vascular remodeling of pulmonary arterial wall, an increased pulmonary vascular resistance, and eventually PH[5,15-17]. Among patients with mitral valve disease in the present study, dyspnea, LA volume index, significant regurgitation of right-sided heart valves, severe disease, and stenotic lesion were independent determinants of PH. These findings emphasize the importance of the pathophysiological alterations of mitral valve disease, such as the severity of clinical disease, LA remodeling and stenotic lesion, leading to PH. The relationship between the New York Heart Association functional class and PH in patients with mitral valve disease has previously been reported[2,18]. The more severe the mitral valve disease, the greater is the expected LA dilatation and the higher pulmonary pressure. The present study showed that MS was a more significant determinant of PH than

Table 1. Baseline characteristics and echocardiographic data in all patients with mitral valve disease and the comparisons between patients with and without pulmonary hypertension

Variables	All patients (n=318)	PH (n=119)	No PH (n=199)	p-value
Clinical data				
Age (years); mean±SD	54.3±15.5	55.6±15.7	53.5±15.3	0.258
Sex: female; n (%)	183 (57.6)	72 (60.5)	111 (55.8)	0.409
Body mass index (kg/m^2); mean±SD	22.8±3.7	22.8±4.0	22.8±3.6	0.983
Systolic BP (mmHg); mean±SD	120.7±18.1	117.7±17.2	122.5±18.4	0.023
Diastolic BP (mmHg); mean±SD	69.2±13.9	68.5±13.9	69.6±13.9	0.516
Heart rate (/minute); mean±SD	74.2±14.6	76.5±16.4	72.9±13.3	0.033
Dyspnea; n (%)	129 (40.6)	65 (54.6)	64 (32.2)	<0.001
Hypertension; n (%)	120 (37.7)	41 (34.5)	79 (39.7)	0.350
Diabetes mellitus; n (%)	31 (9.8)	12 (10.1)	19 (9.6)	0.876
Dyslipidemia; n (%)	93 (29.3)	30 (25.2)	63 (31.7)	0.221
Smoking; n (%)	21 (6.6)	5 (4.2)	16 (8.0)	0.182
History of stroke; n (%)	33 (10.4)	12 (10.1)	21 (10.6)	0.894
History of heart failure; n (%)	67 (21.1)	40 (33.6)	27 (13.6)	<0.001
Betablocker; n (%)	145 (46.5)	59 (50.4)	86 (44.1)	0.278
Digoxin; n (%)	55 (17.6)	27 (23.1)	28 (14.4)	0.050
Diuretic; n (%)	153 (49.0)	78 (66.7)	75 (38.5)	<0.001
Anticoagulant; n (%)	133 (42.6)	67 (57.3)	66 (33.9)	<0.001
Atrial fibrillation; n (%)	137 (43.2)	67 (56.3)	70 (35.4)	<0.001
Echocardiographic data				
Severe disease; n (%)	245 (77.0)	108 (90.8)	137 (68.8)	<0.001
Mitral stenosis; n (%)	106 (33.3)	51 (42.9)	55 (27.6)	0.005
Mitral regurgitation; n (%)	212 (66.7)	68 (57.1)	144 (72.4)	0.005
Right atrial pressure (mmHg); mean±SD	7.8±3.5	9.5±4.0	6.8±2.8	<0.001
Peak TR velocity (m/second); mean±SD	3.1±0.6	3.7±0.5	2.7±0.3	<0.001
PASP (mmHg); mean±SD	47.5±18.2	66.2±15.3	36.3±7.4	<0.001
PAEDP (mmHg); mean±SD	15.3±6.2	20.0±6.4	12.5±4.1	<0.001
Mean PAP (mmHg); mean±SD	27.8±9.9	35.9±8.7	22.6±6.7	<0.001
PVR (Wood unit); mean±SD	3.0±2.4	3.9±3.1	2.4±1.8	<0.001
LV diastolic dimension (mm); mean±SD	52.4±9.0	51.7±10.6	52.8±7.9	0.323
LV systolic dimension (mm); mean±SD	32.3±5.9	32.6±5.9	32.1±5.9	0.460
LV end-diastolic volume (mL); mean±SD	97.4±35.2	98.3±39.0	96.8±32.8	0.720
LV end-systolic volume (mL); mean±SD	32.5±14.4	33.9±16.2	31.7±13.2	0.228
LV ejection fraction (%); mean±SD	66.6±7.2	65.1±7.8	67.4±6.7	0.006
LV mass index (g/m^2); mean±SD	129.9±57.9	137.1±78.0	125.9±42.9	0.196
LA diameter (mm); mean±SD	54.2±10.5	59.6±10.9	50.9±8.9	<0.001
LA volume index (mL/m^2); mean±SD	82.3±45.1	102.2±55.9	70.3±31.9	<0.001
Tricuspid annulus (mm); mean±SD	2.9±0.6	3.2±0.5	2.8±0.5	<0.001
TR vena contracta (mm); mean±SD	4.4±1.9	4.7±2.1	4.2±1.7	0.020
Significant TR; n (%)	76 (24.1)	46 (39.0)	30 (15.2)	<0.001
Significant PR; n (%)	32 (10.2)	22 (18.6)	10 (5.1)	<0.001
TAPSE (mm); mean±SD	21.6±5.2	19.8±5.2	22.6±4.9	<0.001
S'TV (cm/second); mean±SD	11.7±2.4	11.3±2.6	12.0±2.3	0.012

SD=standard deviation; BP=blood pressure; LA=left atrial; LV=left ventricular; PAEDP=pulmonary artery end-diastolic pressure; PAP=pulmonary artery pressure; PASP=pulmonary artery systolic pressure; PH=pulmonary hypertension; PR=pulmonary regurgitation; PVR=pulmonary vascular resistance; S'TV=peak systolic myocardial velocity of lateral tricuspid annulus; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation

p-values are for comparisons between 2 groups

Table 2. Comparisons of baseline characteristics, electrocardiographic and echocardiographic data between patients with mitral stenosis and mitral regurgitation

Variables	Mitral stenosis (n=106)	Mitral regurgitation (n=212)	p-value
Clinical data			
Age (years); mean±SD	50.0±12.4	56.4±16.4	<0.001
Sex: female; n (%)	95 (89.6)	88 (41.5)	<0.001
Body mass index (kg/m^2); mean±SD	22.5±3.8	22.9±3.7	0.429
Systolic BP (mmHg); mean±SD	114.9±16.4	123.6±18.2	<0.001
Diastolic BP (mmHg); mean±SD	66.4±12.9	70.5±14.2	0.011
Heart rate (/minute); mean±SD	72.0±13.8	75.3±14.9	0.06
Dyspnea; n (%)	54 (50.9)	75 (35.4)	0.008
Hypertension; n (%)	28 (26.4)	92 (43.4)	0.003
Diabetes mellitus; n (%)	12 (11.3)	19 (9.0)	0.549
Dyslipidemia; n (%)	30 (28.3)	63 (29.7)	0.794
Smoking; n (%)	4 (3.8)	17 (8.0)	0.151
History of stroke; n (%)	22 (20.8)	11 (5.2)	<0.001
History of heart failure; n (%)	23 (21.7)	44 (20.8)	0.846
Betablocker; n (%)	73 (71.6)	72 (34.3)	<0.001
Digoxin; n (%)	35 (34.3)	20 (9.5)	<0.001
Diuretic; n (%)	61 (59.8)	92 (43.8)	0.011
Anticoagulant; n (%)	83 (81.4)	50 (23.8)	<0.001
Electrocardiographic data			
Atrial fibrillation; n (%)	71 (67.0)	66 (31.3)	<0.001
Right axis deviation; n (%)	19 (17.9)	9 (4.3)	<0.001
Left atrial enlargement; n (%)	23 (21.7)	70 (33.2)	0.081
LV hypertrophy; n (%)	6 (5.7)	95 (45.0)	<0.001
QRS duration (ms); mean±SD	87.8±17.5	95.4±17.1	<0.001
Echocardiographic data			
Severe disease; n (%)	74 (69.8)	171 (80.7)	0.030
Right atrial pressure (mmHg); mean±SD	8.4±3.2	7.5±3.7	0.032
Peak TR velocity (m/second); mean±SD	3.2±0.6	3.0±0.6	0.014
PASP (mmHg); mean±SD	51.1±17.1	45.7±18.5	0.013
PAEDP (mmHg); mean±SD	17.3±5.8	14.3±6.2	<0.001
Mean PAP (mmHg); mean±SD	29.6±9.0	26.9±10.2	0.026
PVR (Wood unit); mean±SD	2.8±3.1	3.1±2.1	0.490
LV diastolic dimension (mm); mean±SD	43.9±6.6	56.7±6.8	<0.001
LV systolic dimension (mm); mean±SD	28.9±4.7	34.0±5.6	<0.001
LV end-diastolic volume (mL); mean±SD	68.6±18.5	111.6±32.8	<0.001
LV end-systolic volume (mL); mean±SD	24.9±8.3	36.3±15.3	<0.001
LV ejection fraction (%); mean±SD	63.9±6.8	67.9±7.0	<0.001
LV mass index (g/m^2); mean±SD	90.4±65.7	146.5±45.1	<0.001
LA diameter (mm); mean±SD	56.2±10.2	53.2±10.6	0.016
LA volume index (mL/m^2); mean±SD	87.4±44.8	79.7±45.2	0.148
Tricuspid annulus (mm); mean±SD	2.9±0.6	2.9±0.6	0.906
TR vena contracta (mm); mean±SD	4.4±1.8	4.4±1.9	0.873
Significant TR; n (%)	30 (28.6)	46 (21.9)	0.192
Significant PR; n (%)	8 (7.7)	24 (11.4)	0.303
TAPSE (mm); mean±SD	19.0±5.2	22.8±4.6	<0.001
S'TV (cm/second); mean±SD	10.4±2.1	12.4±2.3	<0.001

SD=standard deviation; BP=blood pressure; LA=left atrial, LV=left ventricular; PAEDP=pulmonary artery end-diastolic pressure; PAP=pulmonary artery pressure; PASP=pulmonary artery systolic pressure; PH=pulmonary hypertension; PR=pulmonary regurgitation; PVR=pulmonary vascular resistance; S'TV=peak systolic myocardial velocity of lateral tricuspid annulus; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation

p-values are for comparisons between 2 groups

Table 3. Baseline characteristics and echocardiographic data in patients with mitral valve disease and the comparisons regarding the presence or absence of pulmonary hypertension and the subgroups of patients with mitral stenosis and mitral regurgitation

Variables	Mitral stenosis			Mitral regurgitation			PH	No PH
	PH (n=51)	No PH (n=55)	p-value*	PH (n=68)	No PH (n=144)	p-value*	p-value**	p-value***
Clinical data								
Age (years); mean±SD	49.4±14.0	50.6±10.8	0.620	60.2±15.4	54.6±16.6	0.021	<0.001	0.051
Sex: female; n (%)	44 (86.3)	51 (92.7)	0.276	28 (41.2)	60 (41.7)	0.95	<0.001	<0.001
Body mass index (kg/m^2); mean±SD	22.6±4.0	22.5±3.6	0.910	22.9±4.0	22.9±3.6	0.916	0.638	0.512
Systolic BP (mmHg); mean±SD	113.1±15.7	116.6±17.1	0.270	121.2±17.6	124.7±18.4	0.194	0.010	0.006
Diastolic BP (mmHg); mean±SD	65.0±13.8	67.6±12.0	0.313	71.1±13.5	70.3±14.5	0.699	0.018	0.228
Heart rate (/minute); mean±SD	74.9±15.4	69.3±11.5	0.039	77.7±17.1	74.2±13.7	0.112	0.356	0.022
Dyspnea; n (%)	31 (60.8)	23 (41.8)	0.051	34 (50.0)	41 (28.5)	0.002	0.242	0.071
Hypertension; n (%)	10 (19.6)	18 (32.7)	0.126	31 (45.6)	61 (42.4)	0.66	0.003	0.214
Diabetes mellitus; n (%)	5 (9.8)	7 (12.7)	0.635	7 (12.3)	12 (8.3)	0.64	0.930	0.346
Dyslipidemia; n (%)	14 (27.5)	16 (29.1)	0.851	16 (23.5)	47 (32.6)	0.18	0.626	0.630
Smoking; n (%)	1 (2.0)	3 (5.5)	0.619	4 (5.9)	13 (9.0)	0.43	0.032	0.020
History of stroke; n (%)	11 (21.6)	11 (20.0)	0.842	1 (1.5)	10 (6.9)	0.11	<0.001	0.007
History of heart failure; n (%)	14 (27.5)	9 (16.4)	0.166	26 (38.2)	18 (12.5)	<0.001	0.218	0.477
Betablocker; n (%)	31 (63.3)	42 (79.3)	0.074	28 (41.2)	44 (31.0)	0.145	0.018	<0.001
Digoxin; n (%)	16 (32.7)	19 (35.9)	0.734	11 (16.2)	9 (6.3)	0.023	0.037	<0.001
Diuretic; n (%)	32 (65.3)	29 (54.7)	0.276	46 (67.7)	46 (32.4)	<0.001	0.791	0.004
Anticoagulant; n (%)	42 (85.7)	41 (77.4)	0.279	25 (36.8)	25 (17.6)	0.002	<0.001	<0.001
Atrial fibrillation; n (%)	36 (70.6)	35 (63.6)	0.447	31 (45.6)	35 (24.5)	0.002	0.007	<0.001
Echocardiographic data								
Severe disease; n (%)	44 (86.3)	30 (54.6)	<0.001	64 (94.1)	107 (74.3)	0.001	0.202	0.007
Right atrial pressure (mmHg); mean±SD	9.3±3.4	7.6±2.8	0.006	9.7±4.4	6.4±2.7	<0.001	0.545	0.010
Peak TR velocity (m/second); mean±SD	3.6±0.5	2.8±0.3	<0.001	3.8±0.5	2.7±0.3	<0.001	0.078	0.003
PASP (mmHg); mean±SD	64.0±15.5	39.2±6.6	<0.001	67.9±15.0	35.2±7.4	<0.001	0.164	0.001
PAEDP (mmHg); mean±SD	20.1±6.0	14.6±3.9	<0.001	19.9±6.7	11.8±3.9	<0.001	0.860	<0.001
Mean PAP (mmHg); mean±SD	34.2±8.9	25.1±6.7	<0.001	19.9±6.7	11.8±3.9	<0.001	0.062	0.003
PVR (Wood unit); mean±SD	3.6±4.3	2.2±0.5	0.038	4.2±1.7	2.5±2.1	<0.001	0.281	0.267
LV diastolic dimension (mm); mean±SD	42.6±7.4	45.1±5.6	0.049	58.6±6.8	55.8±6.6	0.005	<0.001	<0.001
LV systolic dimension (mm); mean±SD	28.8±4.5	28.9±4.9	0.895	35.4±5.2	33.3±5.7	0.01	<0.001	<0.001
LV end-diastolic volume (mL); mean±SD	67.1±18.5	70.0±18.6	0.422	121.3±33.8	107.0±31.3	0.003	<0.001	<0.001
LV end-systolic volume (mL); mean±SD	24.8±8.8	24.9±7.8	0.947	40.5±17.2	34.3±13.9	0.006	<0.001	<0.001
LV ejection fraction (%); mean±SD	63.0±7.4	64.8±6.2	0.184	66.7±7.8	68.4±6.6	0.089	0.012	0.001
LV mass index (g/m^2); mean±SD	95.4±92.3	85.7±24.1	0.001	164.5±51.7	138.7±39.6	<0.001	<0.001	<0.001
LA diameter (mm); mean±SD	59.4±12.1	53.3±6.9	0.002	59.8±9.9	50.1±9.4	<0.001	0.847	0.010
LA volume index (mL/m^2); mean±SD	103.5±57.6	72.6±19.0	0.001	101.3±55.0	69.5±36.6	<0.001	0.830	0.434
Tricuspid annulus (mm); mean±SD	3.1±0.5	2.7±0.6	0.145	3.3±0.5	2.8±0.5	<0.001	0.253	0.640
TR vena contracta (mm); mean±SD	4.2±1.4	4.6±2.2	0.264	5.1±2.4	3.97±1.4	<0.001	0.022	0.101
Significant TR; n (%)	17 (34.0)	13 (23.6)	0.240	29 (42.6)	17 (12.0)	<0.001	0.341	0.041
Significant PR; n (%)	4 (8.0)	4 (7.4)	1.00	18 (26.5)	6 (4.2)	<0.001	0.011	0.467
TAPSE (mm); mean±SD	17.7±5.0	20.3±5.2	0.012	21.4±4.7	23.5±4.4	0.002	<0.001	<0.001
S'TV (cm/second); mean±SD	10.0±2.4	10.7±1.7	0.087	12.2±2.4	12.5±2.3	0.407	<0.001	<0.001
Mitral stenosis; mean±SD								
MVA - planimetry (cm^2)	0.78±0.23	0.95±0.27	0.002					
MVA - pressure half-time (cm^2)	0.81±0.22	1.05±0.43	0.001					
Pressure half-time (ms)	293.4±96.6	226.4±60.2	<0.001					
Mean transmitral gradient (mmHg)	11.1±3.4	6.7±2.6	<0.001					
Mitral valve score	9.4±1.3	8.8±1.1	0.006					
Leaflet mobility	2.0±0.3	2.0±0.3	0.560					
Valvular thickening	2.0±0.6	1.9±0.4	0.254					
Valvular calcification	2.7±0.6	2.5±0.5	0.017					
Subvalvular thickening	2.8±0.7	2.4±0.6	0.011					
Mitral regurgitation; median (P25 to P75)								
EROA (mm^2)				80.4 (46.9 to 119.6)	53.9 (35.1 to 74.7)	<0.001		
Regurgitant volume (mL)				115.8 (83.6 to 148.2)	85.6 (60.5 to 119.9)	<0.001		

SD=standard deviation; P25 to P75=25th to 75th percentile; BP=blood pressure; EROA=effective regurgitant orifice area; LA=left atrial; LAV=left atrial volume; LVEF=left ventricular ejection fraction; MVA=mitral valve area; PAEDP=pulmonary artery end-diastolic pressure; PAP=pulmonary artery pressure; PASP=pulmonary artery systolic pressure; PH=pulmonary hypertension; PR=pulmonary regurgitation; PVR=pulmonary vascular resistance; RAP=right atrial pressure; S'TV=peak systolic myocardial velocity of lateral tricuspid annulus; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation

* p-values are for the comparisons between patients with and without pulmonary hypertension, ** p-values are for the comparisons between patients with mitral stenosis and mitral regurgitation in the presence of pulmonary hypertension, *** p-values are for the comparisons between patients with mitral stenosis and mitral regurgitation in the absence of pulmonary hypertension

Table 4. Univariate and multivariate factors associated with pulmonary hypertension in patients with mitral valve disease and in the subgroups of mitral stenosis and mitral regurgitation

Factors	Mitral valve disease				Mitral stenosis				Mitral regurgitation			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age	-	-	-	-	-	-	-	-	1.02 (1.01 to 1.04)	0.023	-	-
Dyspnea	2.54 (1.59 to 4.05)	<0.001	2.05 (1.19 to 3.55)	0.010	-	-	-	-	2.51 (1.38 to 4.57)	0.003	-	-
Atrial fibrillation	2.36 (1.48 to 3.75)	<0.001	-	-	-	-	-	-	2.58 (1.40 to 4.76)	0.002	-	-
LVEF	0.96 (0.93 to 0.99)	0.003	-	-	-	-	-	-	0.96 (0.93 to 0.99)	0.003	-	-
Significant TR	3.56 (2.08 to 6.08)	<0.001	2.49 (1.35 to 4.62)	0.004	-	-	-	-	5.47 (2.72 to 10.99)	<0.001	3.70 (1.64 to 8.35)	0.002
Significant PR	4.26 (1.94 to 9.36)	<0.001	4.45 (1.77 to 11.23)	0.002	-	-	-	-	8.16 (3.07 to 21.72)	<0.001	7.19 (2.27 to 22.79)	0.001
TAPSE	0.89 (0.85 to 0.94)	<0.001	-	-	0.90 (0.83 to 0.98)	0.015	-	-	0.90 (0.84 to 0.96)	0.002	-	-
LAV index	1.02 (1.01 to 1.03)	<0.001	1.01 (1.01 to 1.02)	0.001	1.02 (1.01 to 1.04)	0.002	1.02 (1.01 to 1.03)	0.007	1.02 (1.01 to 1.03)	<0.001	1.01 (1.001 to 1.02)	0.032
Severe disease	4.44 (2.23 to 8.85)	<0.001	4.71 (2.14 to 10.35)	<0.001	5.24 (2.01 to 13.65)	0.001	4.16 (1.45 to 11.54)	0.006	5.53 (1.88 to 16.45)	0.002	6.14 (1.78 to 21.30)	0.004
Mitral valve score	-	-	-	-	1.56 (1.12 to 2.16)	0.008	-	-				
Mitral stenosis	1.96 (1.22 to 3.18)	0.006	1.97 (1.11 to 3.49)	0.021	-	-	-	-	-	-	-	-

CI=confidence interval; LAV=left atrial volume; LVEF=left ventricular ejection fraction; OR=odd ratio; PR=pulmonary regurgitation; TAPSE=tricuspid annular plane systolic excursion; TR=tricuspid regurgitation

MR, regardless of clinical symptoms, cardiac rhythm, and the severity of mitral valve disease. As previously recognized, LA volume index and the severity of MR were identified as the independent determinants of PH and had prognostic implications in patients with MR[1,2,19]. However, less has been reported with regard to patients with MS. The present study showed that LA volume index and severe disease were important determinants of PH both in patients with MS and those with MR. The present study findings confirm the importance of LA remodeling to the development of PH in patients with mitral valve disease and supported the fundamental relationship in term of pathophysiological mechanisms.

The present study has limitations. Similar to previous studies, the majority of patients in the present study had a severe disease and the results may not be applicable to patients with milder disease. The present study focused on the determinants of PH in patients with mitral valve disease and the outcome data are not available. The assessment of pulmonary artery pressure in the present study was achieved solely by Doppler echocardiography, not by right heart catheterization. However, the echocardiographic estimation of pulmonary artery pressure had been well-validated and reinforced by the current guideline for the routine clinical practice[11].

Conclusion

PH is a common clinical and pathophysiological consequence of mitral valve disease with a prevalence of 37.4% in the present study. Echocardiography can be a valuable way to assess LA function and the likelihood of PH both in patients with MS and those with MR.

What is already known?

PH is common in patients with mitral valve disease.

What this study adds?

LA volume index and severe mitral valve disease are associated with PH in patients with rheumatic MS and organic MR.

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Conflicts of interest

All authors have no conflict of interest.

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