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

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Abstract

Purpose: The aims of the study were 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).

Methods: Patients with isolated moderate to severe organic mitral valve disease were prospectively enrolled. Pulmonary hypertension (PH) was defined echocardiographically as pulmonary artery systolic pressure > 50 mmHg. Patients with MS who had mitral valve area > 1.5 cm² and patients with MR who had effective regurgitant orifice area < 20 mm² were excluded.

Results: There were 318 patients (mean age 54.3 ± 15.5 years, 57.6% female, 66.7% MR). PH was present in 119 (37.4%) patients (48.1% and 31.8% in MS and MR, respectively). Severe mitral valve disease was reported in 245 (77.0%) patients. 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.

Conclusions: 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.

Introduction

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 23–33% of patients [1–4]. Chronic pressure and volume overload of the left atrium (LA) in patients with mitral valve disease lead 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 > 50 mmHg at rest, is a valuable sign in determining the need for valvular intervention in patients with mitral valve disease [6, 7]. Several previous studies have verified the factors associated with PH (eg. age, LA enlargement, 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 patients with mitral valve disease and, specifically, in the subgroups of patients with MS and MR. The study also evaluated the similarities and differences regarding the echocardiographic findings in patients with MS versus MR.

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 study. Patients with mild MS, defined as a mitral valve area > 1.5 cm² and patients with mild MR, defined as an effective regurgitant orifice area < 20 mm², 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 (left ventricular ejection fraction < 50%), congenital or pericardial disease, renal dysfunction, 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). 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 3–5 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 [9]. The mitral valve anatomy in MS was assessed using Wilkins score [10]. Patients with MS who were found to have a mitral valve area $< 1.0 \text{ cm}^2$, and patients with MR who were found to have an effective regurgitant orifice area $\geq 40 \text{ mm}^2$ and regurgitant volume $\geq 60 \text{ ml}$ were considered to have severe disease (Fig. 1). 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 (Fig. 1) [11]. PH was defined as pulmonary artery systolic pressure $> 50 \text{ mmHg}$ [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 and 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 $\pm$ standard deviation for normally distributed variables and median (25th – 75th 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). For all tests performed, a two-tailed p-value < 0.05 was considered to be statistically significant. PASW Statistic (SPSS) 18.0 (SPSS, Inc., Chicago, IL, USA) was used to perform all statistical analyses.

Results

There were 318 patients enrolled in the study (mean age 54.3 ± 15.5 years) of whom 183 (57.6%) were female. PH was reported in 119 (37.4%) patients. 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.

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)	54.3 ± 15.5	55.6 ± 15.7	53.5 ± 15.3	0.258
Female gender	183 (57.6)	72 (60.5)	111 (55.8)	0.409
Body mass index (kg/m ²)	22.8 ± 3.7	22.8 ± 4.0	22.8 ± 3.6	0.983
Systolic BP (mmHg)	120.7 ± 18.1	117.7 ± 17.2	122.5 ± 18.4	0.023
Diastolic BP (mmHg)	69.2 ± 13.9	68.5 ± 13.9	69.6 ± 13.9	0.516
Heart rate (/min)	74.2 ± 14.6	76.5 ± 16.4	72.9 ± 13.3	0.033
Dyspnea	129 (40.6)	65 (54.6)	64 (32.2)	< 0.001
Hypertension	120 (37.7)	41 (34.5)	79 (39.7)	0.350
Diabetes mellitus	31 (9.8)	12 (10.1)	19 (9.6)	0.876
Dyslipidemia	93 (29.3)	30 (25.2)	63 (31.7)	0.221
Smoking	21 (6.6)	5 (4.2)	16 (8.0)	0.182
History of stroke	33 (10.4)	12 (10.1)	21 (10.6)	0.894
History of heart failure	67 (21.1)	40 (33.6)	27 (13.6)	< 0.001
Betablocker	145 (46.5)	59 (50.4)	86 (44.1)	0.278
Digoxin	55 (17.6)	27 (23.1)	28 (14.4)	0.050
Diuretic	153 (49.0)	78 (66.7)	75 (38.5)	< 0.001
Anticoagulant	133 (42.6)	67 (57.3)	66 (33.9)	< 0.001
Atrial fibrillation	137 (43.2)	67 (56.3)	70 (35.4)	< 0.001
Echocardiographic data				
Severe disease	245 (77.0)	108 (90.8)	137 (68.8)	< 0.001
Mitral stenosis	106 (33.3)	51 (42.9)	55 (27.6)	0.005
Mitral regurgitation	212 (66.7)	68 (57.1)	144 (72.4)	0.005
Right atrial pressure (mmHg)	7.8 ± 3.5	9.5 ± 4.0	6.8 ± 2.8	< 0.001
Peak TR velocity (m/sec)	3.1 ± 0.6	3.7 ± 0.5	2.7 ± 0.3	< 0.001
PASP (mmHg)	47.5 ± 18.2	66.2 ± 15.3	36.3 ± 7.4	< 0.001
PAEDP (mmHg)	15.3 ± 6.2	20.0 ± 6.4	12.5 ± 4.1	< 0.001
Mean PAP (mmHg)	27.8 ± 9.9	35.9 ± 8.7	22.6 ± 6.7	< 0.001
PVR (Wood unit)	3.0 ± 2.4	3.9 ± 3.1	2.4 ± 1.8	< 0.001

Data are expressed as number (%) and mean ± standard deviation.

P-values are for comparisons between 2 groups

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

Variables	All patients (n = 318)	PH (n = 119)	No PH (n = 199)	P-value
LV diastolic dimension (mm)	52.4 ± 9.0	51.7 ± 10.6	52.8 ± 7.9	0.323
LV systolic dimension (mm)	32.3 ± 5.9	32.6 ± 5.9	32.1 ± 5.9	0.460
LV end-diastolic volume (ml)	97.4 ± 35.2	98.3 ± 39.0	96.8 ± 32.8	0.720
LV end-systolic volume (ml)	32.5 ± 14.4	33.9 ± 16.2	31.7 ± 13.2	0.228
LV ejection fraction (%)	66.6 ± 7.2	65.1 ± 7.8	67.4 ± 6.7	0.006
LV mass index (g/m ²)	129.9 ± 57.9	137.1 ± 78.0	125.9 ± 42.9	0.196
LA diameter (mm)	54.2 ± 10.5	59.6 ± 10.9	50.9 ± 8.9	< 0.001
LA volume index (ml/m ²)	82.3 ± 45.1	102.2 ± 55.9	70.3 ± 31.9	< 0.001
Tricuspid annulus (mm)	2.9 ± 0.6	3.2 ± 0.5	2.8 ± 0.5	< 0.001
TR vena contracta (mm)	4.4 ± 1.9	4.7 ± 2.1	4.2 ± 1.7	0.020
Significant TR	76 (24.1)	46 (39.0)	30 (15.2)	< 0.001
Significant PR	32 (10.2)	22 (18.6)	10 (5.1)	< 0.001
TAPSE (mm)	21.6 ± 5.2	19.8 ± 5.2	22.6 ± 4.9	< 0.001
S' _{TV} (cm/sec)	11.7 ± 2.4	11.3 ± 2.6	12.0 ± 2.3	0.012
Data are expressed as number (%) and mean ± standard deviation.				
P-values are for comparisons between 2 groups				
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				

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 31.8% 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 (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.

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)	50.0 ± 12.4	56.4 ± 16.4	< 0.001
Female gender	95 (89.6)	88 (41.5)	< 0.001
Body mass index (kg/m ²)	22.5 ± 3.8	22.9 ± 3.7	0.429
Systolic BP (mmHg)	114.9 ± 16.4	123.6 ± 18.2	< 0.001
Diastolic BP (mmHg)	66.4 ± 12.9	123.6 ± 18.2	0.011
Heart rate (/min)	72.0 ± 13.8	75.3 ± 14.9	0.06
Dyspnea	54 (50.9)	75 (35.4)	0.008
Hypertension	28 (26.4)	92 (43.4)	0.003
Diabetes mellitus	12 (11.3)	19 (9.0)	0.549
Dyslipidemia	30 (28.3)	63 (29.7)	0.794
Smoking	4 (3.8)	17 (8.0)	0.151
History of stroke	22 (20.8)	11 (5.2)	< 0.001
History of heart failure	23 (21.7)	44 (20.8)	0.846
Betablocker	73 (71.6)	72 (34.3)	< 0.001
Digoxin	35 (34.3)	20 (9.5)	< 0.001
Diuretic	61 (59.8)	92 (43.8)	0.011
Anticoagulant	83 (81.4)	50 (23.8)	< 0.001
Electrocardiographic data			
Atrial fibrillation	71 (67.0)	66 (31.3)	< 0.001
Right axis deviation	19 (17.9)	9 (4.3)	< 0.001
Left atrial enlargement	23 (21.7)	70 (33.2)	0.081
LV hypertrophy	6 (5.7)	95 (45.0)	< 0.001
QRS duration (ms)	87.8 ± 17.5	95.4 ± 17.1	< 0.001
Echocardiographic data			
Severe disease	74 (69.8)	171 (80.7)	0.030
Right atrial pressure (mmHg)	8.4 ± 3.2	7.5 ± 3.7	0.032
Peak TR velocity (m/sec)	3.2 ± 0.6	3.0 ± 0.6	0.014
PASP (mmHg)	51.1 ± 17.1	45.7 ± 18.5	0.013

Data are expressed as number (%) and mean ± standard deviation.

P-values are for comparisons between 2 groups

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

Variables	Mitral stenosis (n = 106)	Mitral regurgitation (n = 212)	P-value
PAEDP (mmHg)	17.3 ± 5.8	14.3 ± 6.2	< 0.001
Mean PAP (mmHg)	29.6 ± 9.0	26.9 ± 10.2	0.026
PVR (Wood unit)	2.8 ± 3.1	3.1 ± 2.1	0.490
LV diastolic dimension (mm)	43.9 ± 6.6	56.7 ± 6.8	< 0.001
LV systolic dimension (mm)	28.9 ± 4.7	34.0 ± 5.6	< 0.001
LV end-diastolic volume (ml)	68.6 ± 18.5	111.6 ± 32.8	< 0.001
LV end-systolic volume (ml)	24.9 ± 8.3	36.3 ± 15.3	< 0.001
LV ejection fraction (%)	63.9 ± 6.8	67.9 ± 7.0	< 0.001
LV mass index (g/m ²)	90.4 ± 65.7	146.5 ± 45.1	< 0.001
LA diameter (mm)	56.2 ± 10.2	53.2 ± 10.6	0.016
LA volume index (ml/m ²)	87.4 ± 44.8	79.7 ± 45.2	0.148
Tricuspid annulus (mm)	2.9 ± 0.6	2.9 ± 0.6	0.906
TR vena contracta (mm)	4.4 ± 1.8	4.4 ± 1.9	0.873
Significant TR	30 (28.6)	46 (21.9)	0.192
Significant PR	8 (7.7)	24 (11.4)	0.303
TAPSE (mm)	19.0 ± 5.2	22.8 ± 4.6	< 0.001
S' _{TV} (cm/sec)	10.4 ± 2.1	12.4 ± 2.3	< 0.001
Data are expressed as number (%) and mean ± standard deviation.			
P-values are for comparisons between 2 groups			
<i>BP</i> blood pressure, <i>LA</i> left atrial, <i>LV</i> left ventricular, <i>PAEDP</i> pulmonary artery end-diastolic pressure, <i>PAP</i> pulmonary artery pressure, <i>PASP</i> pulmonary artery systolic pressure, <i>PH</i> pulmonary hypertension, <i>PR</i> pulmonary regurgitation, <i>PVR</i> pulmonary vascular resistance, <i>S'_{TV}</i> peak systolic myocardial velocity of lateral tricuspid annulus, <i>TAPSE</i> tricuspid annular plane systolic excursion, <i>TR</i> tricuspid regurgitation			

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)	49.4 ± 14.0	50.6 ± 10.8	0.620	60.2 ± 15.4	54.6 ± 16.6	0.021	< 0.001	0.051
Female gender	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)	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)	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)	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 (/min)	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	31 (60.8)	23 (41.8)	0.051	34 (50.0)	41 (28.5)	0.002	0.242	0.071
Hypertension	10 (19.6)	18 (32.7)	0.126	31 (45.6)	61 (42.4)	0.66	0.003	0.214
Diabetes mellitus	5 (9.8)	7 (12.7)	0.635	7 (12.3)	12 (8.3)	0.64	0.930	0.346
Dyslipidemia	14 (27.5)	16 (29.1)	0.851	16 (23.5)	47 (32.6)	0.18	0.626	0.630
Smoking	1 (2.0)	3 (5.5)	0.619	4 (5.9)	13 (9.0)	0.43	0.032	0.020
History of stroke	11 (21.6)	11 (20.0)	0.842	1 (1.5)	10 (6.9)	0.11	< 0.001	0.007
History of heart failure	14 (27.5)	9 (16.4)	0.166	26 (38.2)	18 (12.5)	< 0.001	0.218	0.477
Betablocker	31 (63.3)	42 (79.3)	0.074	28 (41.2)	44 (31.0)	0.145	0.018	< 0.001
Digoxin	16 (32.7)	19 (35.9)	0.734	11 (16.2)	9 (6.3)	0.023	0.037	< 0.001
Diuretic	32 (65.3)	29 (54.7)	0.276	46 (67.7)	46 (32.4)	< 0.001	0.791	0.004
Anticoagulant	42 (85.7)	41 (77.4)	0.279	25 (36.8)	25 (17.6)	0.002	< 0.001	< 0.001
Atrial fibrillation	36 (70.6)	35 (63.6)	0.447	31 (45.6)	35 (24.5)	0.002	0.007	< 0.001
Echocardiographic data								
Severe disease	44 (86.3)	30 (54.6)	< 0.001	64 (94.1)	107 (74.3)	0.001	0.202	0.007

Data are expressed as number (%), mean ± standard deviation and median (25th – 75th percentile).

* 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.

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

Variables	Mitral stenosis			Mitral regurgitation			PH	No PH
Right atrial pressure (mmHg)	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/sec)	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)	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)	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)	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)	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)	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)	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)	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)	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 (%)	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)	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)	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)	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)	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)	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	17 (34.0)	13 (23.6)	0.240	29 (42.6)	17 (12.0)	< 0.001	0.341	0.041
Significant PR	4 (8.0)	4 (7.4)	1.00	18 (26.5)	6 (4.2)	< 0.001	0.011	0.467
TAPSE (mm)	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/sec)	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								

Data are expressed as number (%), mean ± standard deviation and median (25th – 75th percentile).

* 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.

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

Variables	Mitral stenosis		Mitral regurgitation	PH	No PH
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					
EROA (mm ²)			80.4 (46.9–12.0)	53.9 (35.1–74.7)	< 0.001
Regurgitant volume (ml)			115.8 (83.6–148.2)	85.6 (60.5–119.9)	< 0.001
Data are expressed as number (%), mean ± standard deviation and median (25th – 75th percentile).					
* 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.					
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					

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. Left atrial 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 (56.3% vs. 35.4%, $p < 0.001$), and in patients with MS than those with MR (67.0% vs. 37.3%, $p < 0.001$).

Factors Associated With Pulmonary Hypertension

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 than 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.

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

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 23–33% was reported in previous studies [1–4]. LA volume index and a severe clinical 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.

Significance Of Pulmonary Hypertension In Mitral Valve Disease

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 and/or pulmonary edema, which greatly 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 > 50 mmHg [6, 7].

Pathophysiological Consequences of Mitral Valve Disease in Association with Pulmonary Hypertension

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 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 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. Our 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.

Study Limitations

The present study has some limitations. Similar to several 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 has been well-validated and reinforced by the current guideline for the routine clinical practice [11].

Conclusions

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.

Abbreviations

LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; PH, pulmonary hypertension

Declarations

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Competing interests

The authors declare that they have no completing interests.

Availability of data and materials

The datasets supporting the conclusions of the study are included within the article. Any additional data will be available on request.

Code availability

Not applicable

Authors' contributions

Nithima Ratanasit: conceived the study, participated in study design and data collection, analyzed and interpreted data, drafted and revised the manuscript; **Khemajira Karaketklang:** performed statistical analysis and the interpretations of data; **Prayuth Rasmeehirun:** participated in data collection, interpreted data, revised the manuscript and prepared figure; **Roongthip Chanwanitkulchai:** participated in data collection and interpretation, and revised the manuscript. All authors read and approved the final manuscript.

Ethical approval and consent to participate

The Siriraj Institutional Review Board approved the study (Certificate of Approval no. 626/2011). An informed consent was obtained from all patients.

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Figures

Figure 1

The Doppler-echocardiographic study in patients with severe mitral regurgitation (upper panel) and severe mitral stenosis (lower panel). Middle panel shows the Doppler echocardiographic assessment of pulmonary artery pressure. Patients with severe mitral valve disease reveal left atrial enlargement and pulmonary hypertension.