European Heart Journal (2011) **32**, 751–759
doi:10.1093/eurheartj/ehq294

Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: A Multicenter Long-term International Study

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Received 15 December 2009; revised 18 June 2010; accepted 23 July 2010; online publish-ahead-of-print 8 September 2010

See page 665 for the editorial comment on this article (doi:10.1093/eurheartj/ehq399)

Aims To determine the frequency, predictors, and outcome implications of pulmonary hypertension (PH) diagnosed by Doppler echocardiography in a large cohort of patients with the homogenous diagnosis of degenerative mitral regurgitation (MR) due to flail leaflets.

Methods and results The Mitral Regurgitation International DAtabase (MIDA) is a registry including patients with MR due to flail leaflets consecutively referred at tertiary centres in Europe and the USA. Between 1987 and 2004, pulmonary artery systolic pressure (PASP) was measured at baseline by Doppler echocardiography in 437 patients (age 67 $\pm$ 11 years; 66% men). Pulmonary hypertension (PASP $>$ 50 mmHg) was observed in 102 patients (23%). Independent predictors of PH were age and left atrial size ($P < 0.0001$). During a mean follow-up of 4.8 $\pm$ 2.8 years, PH was a strong independent predictor of death [adjusted HR 2.03 (1.30–3.18) $P = 0.002$], cardiovascular death [CVD; adjusted HR 2.21 (1.30–3.76) $P = 0.003$], and heart failure [adjusted HR 1.70 (1.10–2.62) $P = 0.018$]. Mitral valve surgery at any time during follow-up (performed in 325 patients, 75%) was beneficial [adjusted HR for death 0.22 (0.14–0.36) $P < 0.001$], but PH was associated with the increased risk of postoperative death and CVD ($P = 0.01$).

Conclusion Pulmonary hypertension is a frequent complication of significant MR due to flail leaflet and is associated with major outcome implications, approximately doubling the risk of death and heart failure after diagnosis. Mitral valve surgery performed during follow-up is beneficial but does not completely abolish the adverse effects of PH once it is established and is particularly beneficial in patients without PH. These data support relieving PH secondary to MR due to flail leaflet, but also careful consideration for mitral surgery before PH is established.

Keywords Mitral regurgitation • Prognosis • Mitral valve surgery • Pulmonary hypertension • Heart failure

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Background

Pulmonary hypertension (PH) is a known but incompletely studied consequence of degenerative mitral regurgitation (MR).[1] The general perception is that it is a serious complication of MR but this awareness is based on little data. Available studies on PH complicating MR are single-centre, characterized by limited sample size,[2] included varying degree of regurgitation[2,3] and addressed only mild PH.[4] The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of valvular heart disease delivered in 1998[5] specified PH as indication for mitral valve (MV) surgery based on one small study mentioning that mildly elevated pulmonary artery pressure is associated with postoperative persistence of left ventricular (LV) enlargement.[6] The updated guidelines by the European Society of Cardiology (ESC) and ACC/AHA do not provide more support for PH as cause of poor outcome.[7,8]

In addition, although invasive measurements of pulmonary artery systolic pressure (PASP) are seldom used for routine surveillance, presentation characteristics and long-term prognostic implications of PH defined using PASP measured by Doppler echocardiography[9–11] in patients with degenerative MR have yet to be defined. These uncertainties are exemplified by the fact that in current guidelines, the recognition[12] and the threshold of PASP recommended for triggering MV surgery[7,8] is largely based on experts' opinion and on little information based on large long-term outcome studies.

The aims of the present study were to investigate—in a large cohort of patients with coherent diagnosis of degenerative MR due to flail leaflet collected in tertiary cardiology centres—(i) the frequency, (ii) the predictors, (iii) the prognostic value, and (iv) the implications on postoperative outcomes of PH diagnosed by Doppler echocardiography. Pulmonary artery systolic pressure was analysed in light of the definition of PH shared by the current guidelines[7,8,12] as well as a continuous variable without pre-specified cut-offs. Flail leaflet was used as a model of pure degenerative MR associated with significant volume overload.[13,14]

Methods

Study design overview

The Mitral Regurgitation International DAtabase (MIDA) is a registry assembled by systematically merging a series of prospectively collected electronic institutional databases, each originally created to optimize echocardiographic reporting. The registry includes consecutive patients from four tertiary centres in Europe (University Hospitals in France—Amiens and Marseille, and Italy—Bologna and Modena) and one centre in the USA (Mayo Clinic, Rochester, MN). The MIDA investigators are listed in the appendix. All patients provided prior informed consent for anonymous publication of their clinical data for scientific research purposes; the study was conducted in accordance with institutional guidelines, national legal requirements, and the revised Helsinki Declaration.

Inclusion and exclusion criteria

Patients were screened for the study if they had degenerative MR with flail leaflet consecutively diagnosed by two-dimensional echocardiography between 1987 and 2004 at one of the participating centres. The general eligibility criteria for entry in the MIDA database were previously described elsewhere.[15] Briefly, patients were enrolled in the presence of (i) an echocardiographic diagnosis of degenerative MR with evidence of flail leaflet[13,16] and (ii) a comprehensive clinical/instrumental evaluation at the time of baseline echocardiography. Patients with ischaemic MR (including papillary muscle rupture), concomitant aortic valve disease, congenital diseases, mitral stenosis, and prior valve surgery were all excluded from the MIDA registry.

Specific inclusion/exclusion criteria for the present analysis were: (i) presence of tricuspid regurgitation allowing measurement of PASP by Doppler echocardiography; (ii) absence of World Health Organization (WHO)[12,17] Group 1 PH (e.g. pulmonary arterial hypertension), Group 3 PH (PH associated with lung respiratory diseases and/or hypoxia), Group 4 PH (PH due to chronic thrombotic and/or embolic disease), and Group 5 PH (PH associated with a miscellaneous of rare diseases) as diagnosed by the referring physician.

Echocardiography

All index transthoracic echocardiograms were performed within routine clinical practice, using standard methods,[18] and prospectively entered in each of the original institutional databases. Severity of MR was assessed semi-quantitatively on a scale from 1 to 4 by Doppler echocardiography.[13,16]

Diagnosis of flail leaflet was based on the failure of leaflet coaptation, with rapid systolic movement of the involved leaflet tip in the left atrium (LA).[13,16]

With continuous-wave Doppler, the maximum peak tricuspid regurgitant velocity (TRV) recorded from any view was used to determine the PASP with the simplified Bernoulli's equation [PASP = 4* (peak TRV)^2 + mean right atrial pressure]; mean right atrial pressure (RAP) was estimated from the respiratory changes of the inferior vena cava diameter with inspiration as follows: complete collapse, RAP = 5 mmHg; partial collapse, RAP = 10 mmHg; and no collapse, RAP = 15 mmHg. Pulmonary artery systolic pressure was assumed to equate the right ventricular systolic pressure in the absence of pulmonic stenosis and right ventricular outflow tract obstruction.[19]

Left ventricular ejection fraction (LVEF) was measured either using LV end-diastolic and systolic diameters by the Quinones method, or using the LV end-diastolic and systolic volumes by the Simpson's method.[18]

Definition of pulmonary hypertension

In keeping with current guidelines,[7,8,12] PH was defined using the prespecified cut-off of PASP >50 mmHg at rest. In the present study, the term PH refers to an increased PASP associated with left heart diseases (Group 2 PH).[12,17]

Follow-up

Overall follow-up extended from baseline clinical/instrumental evaluation until last available contact or death and it was completed in 98% of the patients. The main endpoint was overall survival during the entire follow-up encompassing medical and surgical management. Other endpoints were cardiovascular death (CVD), heart failure requiring hospitalization, survival under medical management (censored at surgery), and postoperative survival in patients who underwent surgery. Cardiovascular death included deaths due to progressive LV dysfunction, acute heart failure, myocardial infarction, endocarditis, prosthesis dysfunction, and thromboembolism. During follow-up, patients were monitored by their referring physicians. Clinical variables were obtained by review of medical records. Events were ascertained by clinical interviews and/or by telephone calls with

physicians, patients, and (if necessary) next of kin. Autopsy records and death certificates were consulted for attribution of cause of death. The decision to operate or not was left to the discretion of the referring physician. Reasons to deny or delay surgery were recorded in every patient when applicable.

Statistical analysis

Continuous variables were expressed as mean value ± 1 standard deviation (SD) and compared with Student's *t*-tests. Categorical variables were summarized as frequency (percentages) and analysed by chi-square tests. Logistic regression analysis was used to test the univariate and multivariable predictors of PH. The entire follow-up was used to analyse overall outcomes under conservative (non-surgical) and surgical treatment. For the analysis of outcomes under conservative (non-surgical) treatment, event rates were calculated considering the entire follow-up of those patients who did not undergo MV surgery or the period from baseline to any MV operation (as appropriate).

Event rates ± 1 standard error (SE) were estimated according to the Kaplan–Meier method and compared with a two-sided log-rank test. Univariate and multivariable analyses of time to events were performed using Cox proportional models with PASP as independent variable in categorical and continuous format. For display purposes, the HR for PASP as a continuous variable is shown for each 10 mmHg increment (i.e. PASP/10). For multivariable analyses, we used predefined Cox proportional hazards multivariable models that included covariates considered of potential prognostic impact [age, sex, presence of symptoms at baseline classified according to the New York Heart Association (NYHA) class, atrial fibrillation (AFib) at baseline, LVEF, and surgery]. The effect of surgery on the outcome was analysed as a time-dependent variable in a Cox multivariable model with the use of data from the entire follow-up. Receiver operating characteristic (ROC) analysis was used to identify the level of PASP that best predicted total and CVD. The area under the curve of ROC curves and integrated discrimination improvement (IDI) comparison were used to assess the predictive ability of multivariable models.

A significance level of 0.05 was assumed for all statistical tests. All *P*-values are results of two-tailed tests. Data were analysed with SPSS 13.0 statistical software (SPSS Inc., Chicago, IL, USA) and SAS statistical software, version 8 (SAS Institute, Cary, NC, USA).

Results

Study population

The inclusion/exclusion criteria were fulfilled by 437 patients (among the 862 currently enrolled in the MIDA Registry); the overall clinical characteristics of the study population are depicted in *Table 1* (left column). The majority of patients presented with no or minimal symptoms and with preserved LVEF. Flail leaflet was attributable exclusively to a degenerative process in 401 patients (92%) and to endocarditis in the remaining 36 (8%). The posterior leaflet was involved in 357 patients (82%), the anterior leaflet in 44 (10%), and both leaflets in 36 (8%).

Baseline characteristics of patients with pulmonary hypertension

Mean PASP was 45 ± 15 mmHg [median (25th–75th percentile) 40.0 mmHg (34–50)]. The 102 (23%) patients with PASP >50 mmHg (*Table 1*) were generally older, more often in AFib, with a more advanced NYHA functional class, and showed larger LA diameter. However, the MR severity and the LV enlargement and function were not different between patients with and without PH. Pulmonary hypertension was not related to insufficient treatment, as medical therapy for symptoms and LV dysfunction was more frequently used in PH patients (*Table 1*). In multivariable analysis, age (adjusted HR = 1.05, 95% CI 1.03–1.08, $P < 0.0001$) and LA size (adjusted HR = 1.06, 95% CI 1.03–1.09, $P < 0.0001$) were independently associated with significantly increased prevalence of PH.

Table 1 Baseline characteristics of the patient population overall and according to the presence of pulmonary hypertension according to current guidelines definition (pulmonary artery systolic pressure >50 mmHg)

	Overall, *n* = 437	PH present, *n* = 102	PH absent, *n* = 335	*P*-value
Age (years)	67.5 ± 11.4	71.8 ± 10.3	66.1 ± 11.4	<0.0001
BSA (m^2)	1.8 ± 0.21	1.79 ± 0.23	1.81 ± 0.20	0.418
Male gender, *n* (%)	290 (66)	60 (59)	230 (69)	0.066
NYHA Classes III–IV, *n* (%)	153 (35.0)	65 (63.7)	88 (26.3)	<0.0001
Atrial fibrillation, *n* (%)	104 (23.8)	37 (36.3)	67 (20.0)	0.001
History of coronary artery disease, *n* (%)	36 (8.2)	11 (10.8)	25 (7.5)	0.285
Left atrial dimension (mm)	51.1 ± 9.5	55.1 ± 10.6	49.9 ± 8.7	<0.0001
Left ventricular end-diastolic dimension (mm)	59.4 ± 8.5	60.3 ± 8.1	59.1 ± 8.6	0.239
Left ventricular end-systolic dimension (mm)	36.5 ± 7.7	36.9 ± 7.7	36.4 ± 7.7	0.612
Left ventricular ejection fraction (%)	64.1 ± 10.1	63.7 ± 10.1	64.2 ± 10.0	0.712
Grade 3–4 MR by Doppler echocardiography, *n* (%)	409 (94.5)	97 (96.0)	312 (94.0)	0.427
ACE-inhibitors/ARB, *n* (%)	219 (50.7)	59 (60.2)	160 (47.9)	0.032
Beta-blockers, *n* (%)	79 (18.2)	18 (18.2)	61 (18.3)	0.985
Digoxin, *n* (%)	144 (33.3)	48 (48.5)	96 (28.7)	0.0002
Diuretics, *n* (%)	203 (47.0)	62 (62.62)	141 (42.3)	0.0003

BSA, body surface area; NYHA, New York Heart Association; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers.

Implications of pulmonary hypertension for outcome after diagnosis

Overall mortality

After diagnosis, follow-up was 4.79 ± 2.8 years [median (25th–75th percentile) 4.55 (2.54–6.79) years], and 101 deaths (23%) were recorded. Thus, the survival rate 1 and 5 years after diagnosis was 96 ± 0.1 and 81 ± 2%, respectively. The Five-year survival rate was higher for patients with PASP ≤50 mmHg (86 ± 2 vs. 63 ± 5%, $P < 0.0001$; *Figure 1A*).

Univariate predictors of death were age, NYHA class, AFib, LVEF, LA size, LV end-diastolic, and end-systolic diameter ($P \leq 0.001$). Treatments with diuretic and digoxin were also univariate predictors of overall mortality ($P \leq 0.002$). In univariate analysis, PASP >50 mmHg was associated with increased risk of death (HR 2.66, 95% CI 1.79–3.96, $P < 0.0001$). In multivariable analysis, after adjustment for age and gender, the presence of PH was independently associated with survival (adjusted HR 2.09, 95% CI 1.39–3.13, $P < 0.001$, ROC for the full model 0.731); the same result was obtained with PASP as a continuous variable (adjusted HR 1.18, 95% CI 1.06–1.32, $P = 0.002$, ROC for the full model 0.724). After multivariable adjustment for age, gender, NYHA class, AFib, LVEF, and surgery as a time-dependent variable (*Table 2*), PASP >50 mmHg as well as PASP as a continuous variable remained both associated with a significantly increased risk of death with a risk ratio which remained unchanged (*Table 2*). Notably, in the latter multivariable analysis, the addition of PASP > 50 improved the predictive ability of the model (ROC 0.763 for the full model vs. 0.747 for the restrictive model, at IDI analysis $P = 0.014$). Pulmonary artery systolic pressure >50 mmHg was associated with excess mortality in patients with NYHA class I or II at presentation (HR 3.29, 95% CI 1.81–5.96, $P < 0.0001$) or class III or IV (HR 2.00, 95% CI 1.09–3.69, $P = 0.025$) and in those with EF <60% (HR 3.11, 95% CI 1.50–6.43, $P = 0.002$) or those with EF ≥60% (HR 2.38, 95% CI 1.46–3.87, $P = 0.0004$). When MV surgery was factored into the model containing all of the independent predictors of death, surgical treatment as a time-dependent variable was an independent and favourable predictor of prognosis (adjusted HR 0.22, 95% CI 0.14–0.36, $P < 0.0001$). When MV surgery was factored in the multivariable model as a three-level variable (no surgery, MV repair, or MV replacement), both MV repair and MV replacement were associated with a significantly reduced risk of death (HR 0.20, 95% CI 0.12–0.34, $P < 0.001$ and HR 0.28, 95% CI 0.15–0.54, $P < 0.001$, respectively). The association between PASP >50 mmHg as well as PASP as a continuous variable and death remained significant both when the surgery was entered as a two-level (*Table 2*) and as a three-level variable ($P = 0.005$) (data not shown). After further adjustment for left atrial size and LV end-systolic dimension, the strong association between PH or PASP remained unaffected and the risk ratio for death did not change (adjusted HR 1.94, 95% CI 1.23–3.06, $P = 0.004$, and adjusted HR 1.15, 95% CI 1.02–1.30, $P = 0.024$, respectively).

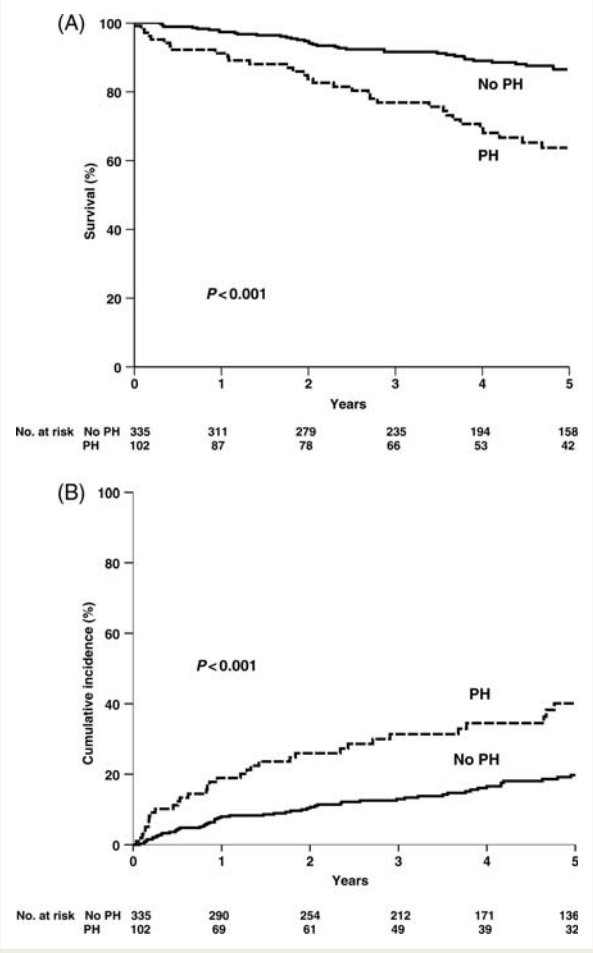

Figure 1 Survival curves according to a cut-off value of pulmonary artery systolic pressure >50 mmHg in patients with mitral regurgitation due to flail leaflets under medical and surgical management. The selected endpoints are (*A*) overall mortality and (*B*) cumulative incidence of heart failure.

We performed ROC analyses testing PASP to define the cut-off best associated with outcome. A PASP cut-off value of 45 mmHg was associated with 60% sensitivity and 73% specificity, while 50 mmHg was characterized by a 41% sensitivity and 82% specificity for overall mortality.

In the overall population, there were 13 sudden deaths, 8 (61.5%) in patients who were treated medically and 5 (38.5%) in those who underwent surgery, $P = 0.003$. The risk of sudden death was significantly lower in patients who underwent surgery compared with those who were treated medically (HR 0.13, 95% CI 0.04–0.45, $P = 0.001$).

Cardiovascular mortality

Among the 101 deaths recorded after diagnosis, 72 were CVDs. At 5 years, the CVD rate was overall 14 ± 2% (8 ± 2% for patients with PASP ≤50 mmHg and 32 ± 5% for patients with PASP >50 mmHg, $P < 0.0001$). In the univariate analysis, PASP >50 mmHg was associated with increased risk of CVD (HR 3.28, 95% CI 2.05–5.25, $P < 0.0001$). On the multivariable analysis, after adjustment for age and gender, PASP >50 mmHg as well as PASP as a continuous variable were independently associated with CVD (adjusted HR 2.43, 95% CI 1.51–3.92, $P < 0.001$, ROC 0.744 and adjusted HR 1.21, 95% CI 1.06–1.37, $P = 0.003$, ROC 0.735,

Table 2 Relative risk of overall death, cardiovascular death, and cumulative incidence of heart failure associated with pulmonary hypertension compared with patients without pulmonary hypertension (results of Cox multivariable analyses and c-statistic of multivariable models)

	PASP > 50 mmHg (categorical variable)			PASP per 10 mmHg increase (continuous variable)		
	HR (95% CI)	*P*-value	ROC	HR (95% CI)	*P*-value	ROC
Overall death						
Adjusted for age, gender, symptoms, LVEF, AFib, and MV surgery	2.03 (1.30–3.18)	0.002	0.665	1.16 (1.03–1.31)	0.013	0.665
Death from cardiovascular causes						
Adjusted for age, gender, NYHA Class, LVEF, AFib, and MV surgery	2.21 (1.30–3.76)	0.0003	0.711	1.15 (1.00–1.32)	0.0042	0.709
Heart failure						
Adjusted for age, gender, symptoms, LVEF, AFib, and MV surgery	1.70 (1.10–2.62)	0.018	0.515	1.19 (1.06–1.35)	0.004	0.516

AFib, atrial fibrillation; LVEF, left ventricular ejection fraction; MV, mitral valve; PASP, derived pulmonary artery systolic pressure, PH, pulmonary hypertension (PASP >50 mmHg).

respectively). After adjustment for age, gender, NYHA Class, AFib, LVEF, and surgery, PASP >50 mmHg remained associated with a significantly increased risk of CVD; the same applied for PASP as a continuous variable (*Table 2*). The addition of PH to this multivariable model improved its accuracy (ROC for the full model 0.796 vs. 0.785 for the restrictive model, IDI $P = 0.018$). The strong association between PH and CVD persisted both when surgery was entered as a two-level (*Table 2*) and as a three-level variable ($P = 0.010$) (data not shown). When MV surgery was factored into the model containing all of the baseline predictors of CVD, surgical treatment at any time during follow-up was an independent and favourable predictor of CVD (adjusted HR 0.22, 95% CI 0.12–0.39, $P < 0.0001$ for both types of surgery, HR 0.17, 95% CI 0.09–0.34, $P < 0.001$ for repair, and HR 0.33, 95% CI 0.16–0.69, $P = 0.03$ for replacement). Further adjustment for left atrial size and LV end-systolic dimension did not affect the risk ratio of PASP > 50 mmHg for CVD (HR 2.18, 95% CI 1.27–3.72, $P = 0.005$) as well as PASP (adjusted HR 2.18, 95% CI 1.27–3.72, $P = 0.052$). Pulmonary artery systolic pressure >50 mmHg was associated with excess CVD in patients with NYHA class I or II at presentation (HR 3.69, 95% CI 1.77–7.73, $P < 0.0001$) or class III or IV (HR 2.45, 95% CI 1.22–4.94, $P = 0.012$).

At ROC analysis, for CVD, a cut-off value of PASP of 45 mmHg showed a 62% sensitivity and 71% specificity (46% sensitivity and 81% specificity selecting a cut-off of 50 mmHg).

Heart failure

Following diagnosis, 104 patients presented with congestive heart failure. Cumulative incidence of heart failure was higher in patients with PASP >50 mmHg (HR 2.25, 95% CI 1.50–3.36, $P < 0.0001$; *Figure 1B*). Higher values of PASP were associated with increased risk of heart failure (HR 1.02, 95% CI 1.01–1.04, $P < 0.0001$). On the multivariable analysis, after adjustment for age and gender, PASP >50 mmHg and higher PASP (as continuous variable) were independently associated with increased risk of heart failure (adjusted HR 1.82, 95% CI 1.21–2.74, $P = 0.004$, ROC 0.649 and adjusted HR 1.20, 95% CI 1.07–1.34, $P = 0.002$, ROC 0.649, respectively). On the multivariable analysis (*Table 2*), after adjustment for age, gender, NYHA class, AFib, LVEF, and surgery as a time-dependent variable (*Table 2*), PASP >50 mmHg as well as higher PASP (continuous variable) remained associated with significantly increased risk of heart failure both when surgery was considered a two-level variable (*Table 2*) as well as a three-level variable ($P = 0.03$) (data not shown). Surgery was associated with the reduced risk of heart failure (HR 0.32, 95% CI 0.19–0.53, $P < 0.001$ for repair, HR 0.35, 95% CI 0.18–0.19, $P = 0.002$ for replacement, and HR 0.33, 95% CI 0.20–0.53 for both surgery, $P < 0.001$). The addition of PASP >50 mmHg to the multivariable model including age, gender, NYHA class, AFib, LVEF, and surgery improved the predictive accuracy (ROC for the full model 0.709 vs. 0.679 for the restrictive model).

The strong association between PASP and heart failure remained after further adjustment for left atrial size and LV end-systolic diameter (HR 1.73 95% CI 1.11–2.69, $P = 0.015$ for PASP > 50 mmHg, and adjusted HR 1.20 95% CI 1.06–1.35 $P = 0.004$ for PASP as continuous variable).

Prognostic implications of pulmonary hypertension under conservative management

Overall mortality, cardiovascular death, and heart failure

Under conservative (i.e. non-surgical) management 53 patients died, and 38 deaths were CVDs. Estimated 5-year survival rate was 71 ± 5%. Survival rate was higher for patients with PASP ≤50 mmHg (*Figure 2A*). Pulmonary artery systolic pressure >50 mmHg was associated with more than six-fold increased risk of death from any cause (HR = 6.46, 95% CI 3.57–11.71, $P < 0.0001$). Survival free from CVD was higher for patients with PASP ≤50 mmHg. Pulmonary artery systolic pressure >50 mmHg was associated with more than eight-fold increased risk of CVD (HR 8.92, 95% CI 4.34–18.35, $P < 0.0001$). Under medical management, 56 patients were hospitalized because of heart failure. Cumulative incidence of heart failure was higher in patients with PASP >50 mmHg (HR 3.39, 95% CI 1.86–6.20, $P < 0.0001$) (*Figure 2B*). Higher values of PASP were associated with increased risk of heart failure (HR 1.04, 95% CI 1.02–1.06, $P < 0.0001$).

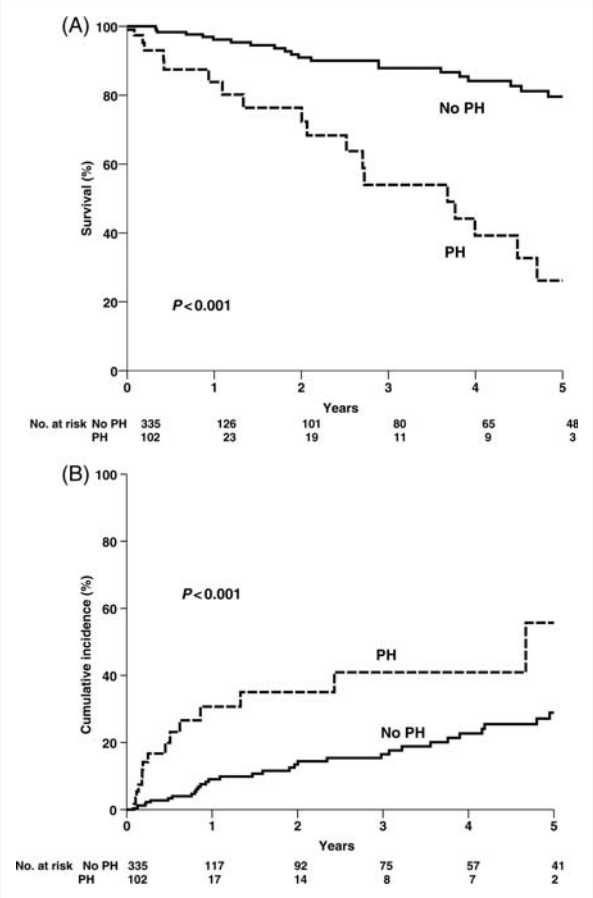

Figure 2 Survival curves according to pulmonary artery systolic pressure >50 mmHg in patients with mitral regurgitation due to flail leaflets under conservative (i.e. non-surgical) management. The selected endpoints are (*A*) overall mortality and (*B*) cumulative incidence of heart failure.

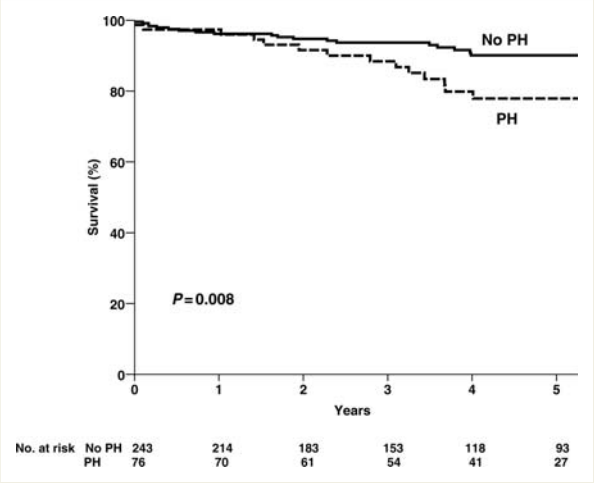

Figure 3 Postoperative survival curves showing overall mortality according to a cut-off value of pulmonary artery systolic pressure >50 mmHg in patients with mitral regurgitation due to flail leaflets.

Pulmonary hypertension and postoperative outcomes

Mitral valve surgery was eventually performed in 325 patients (74.4%). The median time (25th–75th percentile) from the baseline echocardiogram to the operation was 1.8 (0.5–6.4) months. Of the 112 patients who did not undergo surgery, 7 (6.3%) refused surgery, in 10 (9%) patients surgery was denied due to comorbidity, in 11 (9.8%) due to physician preference, in 41 (36.6%) because the patients were relatively well with medical therapy, in 8 (7.1%) because the degree of MR was judged not severe but just moderate to severe, and in 4 (3.6%) due to other reasons. In 31 (27.7) patients, the reason was not clearly specified in the clinical charts, 27 (87%) of these patients had few symptoms (NYHA classes I and II). The MV was repaired in 254 (78%) patients and MV surgery was associated to a coronary artery by-pass graft in 56 (17%). Patients who underwent repair were similar to patients who underwent replacement for all baseline variables shown in *Table 1* except for body surface area. Patients who underwent repair had larger body surface area compared with patients who underwent replacement (1.82 $\pm$ 0.22 vs. 1.76 $\pm$ 0.16 m^2, $P = 0.015$). Operative mortality (defined as death within 30 days from the operation) was 0.6% (two patients). Among the 325 patients who underwent surgery, 102 (31.4%) had PASP $\leq$50 mmHg at baseline. The presence of PH was associated with significantly increased risk of postoperative mortality (HR 2.15, 95% CI 1.20–3.83, $P = 0.01$) (*Figure 3*) and CVD (HR 2.46, 95% CI 1.24–4.88, $P = 0.01$). The results were the same when the analysis was restricted to patients who underwent surgery within 90 days of the diagnosis ($P = 0.04$).

Discussion

The main findings of the present study are that (i) Doppler-derived PH is frequent at rest in patients with MR due to flail leaflet referred to tertiary cardiology centres, (ii) PASP >50 mmHg (the cut-off recommended by the current guidelines to trigger surgery) is independently associated with higher rates of death, CVD, and heart failure, (iii) MV surgery is beneficial independently of the values of PASP, but does not completely abolish the adverse effects of PH once this is established.

Frequency and clinical correlates of pulmonary hypertension

To our knowledge, this is the first study enrolling a large cohort of patients with degenerative MR due to flail leaflet which provides data on the frequency and severity of PH measured by Doppler echocardiography.[10,20] We found that almost a quarter of patients (23%) presented PH according to current guidelines. Although comparative epidemiological data are not available, the prevalence of PH in chronic degenerative MR increases with the severity of the defect and of the symptoms similarly to other left-side valvular diseases.[21]

In our study, the only baseline characteristics independently associated with PH were older age and larger LA diameters.

In degenerative MR, the mechanism leading to PH is complex.[22] In addition to volume overload to the LA which causes a passive pulmonary venous hypertension, in some patients, a superimposed active component caused by pulmonary arterial vasoconstriction and vascular remodelling may contribute to the increase of pulmonary artery pressure.[23] Accordingly, the association we found between cardiac enlargement and PH is not surprising.[22] Recently, Saraiva *et al.*[24] in a cohort of patients with chronic-isolated organic MR demonstrated that LA volume by real-time 3D echocardiography was larger in patients with elevated PASP than in patients with normal PASP and that active LA function was inversely related to PASP, indicating that LA contractile dysfunction may contribute to pulmonary congestion and development of PH.

The other independent predictor of PH turned out to be age. The correlation between age and PASP has been recently noted in a large population-based study, and is likely related to the age-induced impairment of diastolic function.[25,26] Of note, earlier pathology studies suggested that age can also contribute to the rise of PASP by increasing the medial thickness of the vessels eventually impairing their elastic properties.[27–29]

Pulmonary hypertension and outcome

Our data show a relationship between the value of PASP measured by Doppler echocardiography at rest and the risk of subsequent major cardiovascular adverse events. Besides the possibility that PH could represent only a marker of severity of the underlying left heart disease, abnormal values of PASP could independently affect prognosis by inducing right ventricular dysfunction[30] and subsequent functional tricuspid regurgitation.[31] Furthermore, previous studies suggested that PH can exert direct unfavourable effects on prognosis via neurohumoral activation,[32] and/or impairment of pulmonary ventilation.[33]

Pulmonary hypertension, surgery, and postoperative outcomes

Previous reports have shown that preoperative symptoms,[34] arrhythmias,[35] and echocardiographic assessment of decreased ventricular function[36] are predictors of postoperative outcome in patients undergoing surgical correction of organic MR. However, to date the impact of preoperative PASP measured by Doppler echocardiography in these patients has not been reported.

While mitral surgery[37] performed after diagnosis is associated with beneficial impact on outcome, including overall death, CVD, sudden death, and heart failure, nevertheless PH retained a negative prognostic significance, considerable under medical management but also significant after surgery. From a clinical perspective, these results suggest that surgery is associated with an improvement of outcome in patients without PH, but also in those who have already developed PH, both in terms of total mortality, CVD, and incidence of heart failure. Yet, the best postsurgical outcome was observed in patients without PH.

Clinical implications

Although Doppler-derived PASP estimation may be inaccurate in the individual patient[38] and should not replace the cardiac catheterization for definitive haemodynamic assessment of known or suspected PH,[23] echocardiography represents an essential diagnostic tool for the assessment of PH in patients with chronic MR.[7,8] The recent guidelines for the diagnosis and treatment of PH delivered by the ESC suggest that the presence of PH by haemodynamic assessment is likely when Doppler-calculated PASP at rest is >50 mmHg.[12] Accordingly, Doppler-derived PASP >50 mmHg complicating severe organic MR probably reflects the presence of PH by right heart catheterization and is associated with an increased risk of adverse events independently of all other baseline characteristics. Therefore, patients presenting this risk factor may be referred for MV surgery even if asymptomatic and with normal ventricular function. On the clinical ground, these results also suggest that MV repair should be considered before the occurrence of PH. This is similar to the current approach of performing MV repair before the occurrence of LV dysfunction.[39]

Strengths and limitations

In regard to internal validity of the study, strengths include the large and homogenous sample of patients with significant degenerative MR of uniform aetiology collected at multiple centres, the numerous covariates included, and the relatively high number of events encountered.

Although we acknowledge that the reproducibility of Doppler estimation of PASP is more limited than that one achievable by other techniques (specifically right heart catheterization), echocardiography nowadays represents the tool most commonly used in clinical practice for routine surveillance of patients with valvular diseases.[40] The current literature reports that right-sided heart pressures can be obtained non-invasively in approximately 60% of patients,[41] which is close to what was observed in the present study (56%).

Quantitative assessment of MR severity by Doppler echocardiography was not universally available, but the inclusion of patients with flail leaflets has likely prevented from enrolling patients with mild degree of regurgitation as >90% of patients were diagnosed with severe MR. While elevated pulmonary pressure is associated with poor outcome, it is uncertain whether right ventricular function and degree of tricuspid regurgitation, which may complicate the course of PH, play a role in influencing outcome, an issue that should be addressed in future studies, now that the independent prognostic role of PH has been demonstrated by the present study.

We did not collect key routine measures used in the evaluation of LA dimensions, such as indexed LA volume. We recognized that the study is a retrospective analysis of prospectively recorded data.

We did not perform exercise Doppler echocardiography to identify cases with PH during exercise. The recommendation for intervention in asymptomatic patients with chronic MR and exercise-induced PASP >60 mmHg[8] is not uniformly accepted due to the lack of large-scale confirmatory data.[12] In addition, peak exercise PASP can reach values >60 mmHg in many healthy individuals older than 60 years.[42]

Patients with PH due to overt causes other than MR were excluded from the present study, but other conditions contributing to PH (WHO Group 1, 3, 4, 5 PH) may be subtle. Nevertheless, the relationships between PH and left heart size and function are

reassuring regarding the strong link between the MR and the occurrence of PH.

In the present study, we tested the prognostic implications of PH using the cut-off of PASP at 50 mmHg, widely recommended to recognize PH[12] and advocate surgery for degenerative MR by the ACC/AHA and ESC Guidelines.[7,8] Our study shows that this threshold (PASP >50 mmHg) is indeed an independent predictor of total mortality, CVD, and heart failure. However, beyond this intuitive threshold, we analysed the whole spectrum of PH severity,[4] and performed ROC analyses testing PASP to define the cut-off best associated with outcome. We found that the cut-off which best predicted death in this population was close to the cut-off indicated in current guidelines and that there is no rationale to recommend surgery with higher PASP. The reliability of Doppler echocardiography to discriminate 45–50 mmHg in PASP is questionable.[29] The consistency of any operator's ability to discriminate this closely even just 5 mmHg is hard to imagine. Therefore, the ROC analysis confirms the major prognostic implication of the cut-off (50 mmHg) proposed by the current guidelines.

In regard to external validity, the results of the present study are mainly applicable to chronic MR due to flail leaflet with detectable tricuspid regurgitation jet by Doppler echocardiography. Flail leaflet most frequently leads to acute MR or acute increase in the severity of MR. This specific haemodynamic burden can induce distinctive structural changes in pulmonary veins and arterioles. Therefore, the frequency and clinical consequences of PH can be different in organic MR without flail leaflet.

When compared with patients consecutively enrolled in the MIDA but without measurable PASP ($n = 342$), our study population tended to be older (67.5 ± 11.4 vs. 62.1 ± 12.7 years, $P < 0.0001$), with smaller body surface area (1.80 ± 0.21 vs. 1.85 ± 0.22 m^2, $P = 0.007$), higher prevalence of symptoms (NYHA classes III–IV: 35.0 vs. 21.9%, $P < 0.0001$) and more frequent AFib at baseline (23.8 vs. 14.6%, $P = 0.001$), worse LVEF (64.1 ± 10.0 vs. 66.0 ± 9.4% $P = 0.006$), and larger LA (51.1 ± 9.4 vs. 49.1 ± 8.5 mm, $P = 0.006$). MIDA patients who did not have measurable PASP had a significantly better survival than our study cohort (unadjusted HR for death 0.57, 95% CI 0.42–0.78, $P < 0.0001$). Patients without measurable pulmonary pressure compared with those without PH were younger (62.1 ± 12.7 vs. 66.1 ± 11.4 years, $P < 0.001$), had larger body surface area (1.85 ± 0.22 vs. 1.81 ± 0.20 m^2, $P = 0.043$), greater LVEF (66 ± 9 vs. 64 ± 10%, $P = 0.015$), and less frequently grade 3 and 4 MR (87 vs. 95%, $P = 0.003$). Survival of patients with PASP ≤50 mmHg was similar to that of patients who did not have measurable PASP (unadjusted HR for death 1.32, 95% CI 0.93–1.87, $P = 0.125$, age-adjusted HR for death 0.97, 95% CI 0.68–1.38, $P = 0.860$).

Conclusion

Pulmonary hypertension is a frequent complication of organic MR due to flail leaflet and is related to the consequences of volume overload on left heart size and function. Doppler estimation of PASP >50 mmHg at rest is an independent predictor of total mortality, CVD, and cumulative incidence of heart failure under surgical and non-surgical management. Mitral valve surgery (mostly repair) performed at any time during follow-up is safe and independently associated with a reduced risk of total mortality and CVD in every sub-set of patients. Nevertheless, the most favourable postsurgical outcome was observed in patients who underwent MV surgery before the occurrence of PH. These findings support early consideration for surgery when repair is feasible, before the occurrence of PH.

Funding

The present study was supported by a grant from the University of Bologna.

Conflict of interest: none declared.

Appendix

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