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Echocardiographic Predictors of Adverse Short-term Outcomes after Heart Surgery in Patients with Mitral Regurgitation and Pulmonary Hypertension

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ABSTRACT

Background: Pulmonary hypertension (PH) is a frequent occurrence and a negative prognostic indicator in patients with mitral regurgitation. Preoperative PH causes higher early and late mortality rates after heart surgery, adverse cardiac events, and postoperative systolic dysfunction in the left ventricle (LV).

Methods: The research consisted of a retrospective study of a group of 171 consecutive patients with mitral regurgitation and preoperative PH who had undergone mitral valve surgery between January 2008 and October 2011. The PH diagnosis was based on echocardiographic evidence (systolic pulmonary artery pressure [sPAP] >35 mm Hg). The echocardiographic examination included assessment of the following: LV volume, LV ejection fraction (LVEF), sPAP, right ventricular end-diastolic diameter, right atrium area indexed to the body surface area, the ratio of the pulmonary acceleration time to the pulmonary ejection time (PAT/PET), tricuspid annular plane systolic excursion (TAPSE), determination of the severity of the associated tricuspid regurgitation, and presence of pericardial fluid. Surgical procedures consisted of mitral valve repair in 55% of the cases and mitral valve replacement in the remaining 45%. Concomitant coronary artery bypass grafting (CABG) surgery was carried out in 52 patients (30.41%), and De Vega tricuspid annuloplasty was performed in 29 patients (16.95%). The primary end point was perioperative mortality. The secondary end points included the following: pericardial, pleural, hepatic, or renal complications; the need for a new surgical procedure; postoperative mechanical ventilation >24 hours; length of stay in the intensive care unit; duration of postoperative inotropic support; need for an intra-aortic balloon pump; and need for pulmonary vasodilator drugs.

Results: The mortality rate was 2.34%. In the univariate analysis, the clinical and echocardiographic parameters associated with mortality were preoperative New York Heart Association (NYHA) class IV, the PAT/PET ratio, TAPSE, the indexed area of the right atrium, and concomitant CABG surgery. In the multivariate analysis, the indexed area of the right atrium and concomitant CABG surgery remained statistically significant. The multivariate analysis also showed the indexed area of the right atrium, LVEF, presence of pericardial fluid, preoperative NYHA class, and concomitant CABG surgery as statistically significant for the secondary end point. The receiver operating characteristic (ROC) curves identified an sPAP value >65 mm Hg to have the highest specificity and sensitivity for the risk of perioperative death in mitral regurgitation patients (area under the ROC curve [AUC], 0.782; $P < .001$) and identified an sPAP value of 60 mm Hg as the secondary end point (AUC, 0.82; $P < .001$). Severe PH (sPAP >60 mm Hg) is associated with a significant increase in the mortality rate; a longer stay in the intensive care unit; a mechanical ventilation duration >24 hours; lengthy inotropic support; renal, hepatic, and pericardial complications; and a need for endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and/or prostanoids, both in the general group and in patients with preserved systolic functioning of the left ventricle.

Conclusions: PH is a strong short-term negative prognostic factor for patients with mitral regurgitation. The surgical procedure should be performed in the early stages of PH. Echocardiographic examination has useful, simple, and reproducible tools for classifying operative risks. An ischemic etiology and a need for concomitant CABG surgery are additional risk factors for patients with mitral regurgitation and PH.

INTRODUCTION

Pulmonary hypertension (PH) is a frequent occurrence and a negative prognostic indicator in patients with mitral valve regurgitation. The impact of PH on the prognosis of patients with mitral regurgitation has been thoroughly debated over the last few years, and there has been increasingly reliable evidence that preoperative PH is associated with postoperative systolic dysfunction of the left ventricle (LV) [Yang 2006], cardiovascular and overall mortality after surgery [Le Tourneau 2010], adverse cardiac events [Kainuma 2011], and operative and late mortality [Ghoreishi 2011]. The American College of Cardiology and the American Heart Association

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(ACC/AHA) recommend mitral valve surgery for asymptomatic patients with severe mitral regurgitation, a preserved LV function, and PH (defined as a systolic pulmonary artery pressure [sPAP] >50 mm Hg at rest or >60 mm Hg with exercise [class IIa, level of evidence C]) [Bonow 2006]. The European Society of Cardiology (ESC) guidelines also recommend surgery for asymptomatic patients with a preserved LVEF and PH (class IIa, level of evidence C) and consider progressive development of PH to be a marker for a poor prognosis after cardiac surgery [Vahanian 2007].

The purpose of our research was to identify clinical and echocardiographic parameters associated with a poor prognosis for postoperative evolution in patients with mitral regurgitation and PH.

MATERIALS AND METHODS

Population

The research consisted of a retrospective study of a group of 171 consecutive patients with mitral regurgitation who had undergone mitral valve surgery between January 2008 and October 2011 and who were known to have PH before the surgery. Our study was approved by the ethics committee of the institution. PH diagnosis was based on echocardiographic evidence (sPAP >35 mm Hg). The exclusion criteria were as follows: mitral valve stenosis or mitral valve disease with predominant stenosis, concomitant significant aortic valve disease requiring a concomitant surgical procedure, and structural tricuspid valve anomalies.

Echocardiographic Measurements

The preoperative transthoracic echocardiographic examination was conducted with a Vivid E9 ultrasound system (GE Healthcare, Piscataway, NJ, USA) or an ACUSON Sequoia C512 system (Siemens Medical Solutions, Malvern, PA, USA). The echocardiographic examination included assessment of the LV volume and LV ejection fraction (LVEF) via the biplane Simpson method; sPAP measurement by evaluation of the maximum tricuspid regurgitation velocity via continuous-wave Doppler; determination of the right ventricular end-diastolic diameter; calculation of the right atrium area (measured in the apical 4-chamber view) indexed for body surface area; pulsed-wave Doppler analysis of the pulmonary valve and calculation of the pulmonary acceleration time (PAT), the pulmonary ejection time (PET), and their ratio; tricuspid annular plane systolic excursion (TAPSE) assessment; the severity of the associated tricuspid regurgitation (on a scale from 1 to 4, depending on the color jet area); and presence of pericardial fluid.

Surgical Procedures

Surgical procedures were conducted with standard cardiopulmonary bypass and consisted of mitral valve repair in 94 (55%) of the cases and mitral valve replacement in 77 cases (45%). Mitral valve repair was carried out via neochordal insertion (for both the anterior and posterior mitral leaflet), quadrangular resection of the posterior mitral leaflet, triangular resection, anterior mitral leaflet augmentation, commissuroplasty, complete or incomplete annuloplasty with an annular ring, resection, and closing of perforations. All mitral valve replacements were carried out with preservation of the subvalvular mitral apparatus. In patients with ischemic mitral regurgitation, mitral valve repair was performed in 36 cases (94.73%). Concomitant CABG surgery was conducted in 52 patients (30.41%), and De Vega tricuspid annuloplasty was performed in 29 patients (16.95%). The mean (SD) number of grafts in patients with ischemic mitral regurgitation was 2.63±0.78, whereas the mean number of grafts in patients with organic mitral regurgitation and associated coronary conditions was 1.64±0.63.

End Points

The primary end point was perioperative mortality. The secondary end points included the following: pericardial, pleural, hepatic, and renal complications; need for a new surgical procedure; postoperative mechanical ventilation >24 hours; length of intensive care unit stay; duration of postoperative inotropic support; need for an intra-aortic balloon pump; need for pulmonary vasodilator drugs (endothelin receptor antagonists [ERAs], phosphodiesterase type 5 inhibitors [PDE5Is], or prostanoids). We defined renal complications as an increase in serum creatinine of 0.3 mg/dL or 50% in <48 hours, hepatic complications as hepatic cytolysis syndrome and/or a spontaneous international normalized ratio >1.5, pleural complications as significant pleurisy necessitating thoracentesis, and pericardial complications as a large amount of pericardial fluid with signs of compression and/or a need for surgical reintervention.

Statistical Analysis

We used MedCalc software (version 12.1.3; MedCalc Software, Mariakerke, Belgium) for statistical analyses. Continuous variables were expressed as the mean±SD. Analysis of variance was used to compare continuous variables, and we used the 2 test or the Fisher exact test for categorical variables. Univariate and multivariate regression analysis (with a backwards elimination model) were used to evaluate the prognostic value of variables. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cutoff value for sPAP with respect to prognosis. For all analyses, a P value <.05 was considered statistically significant.

RESULTS

Mitral valve regurgitation was functional (ischemic) in 38 (22.22%) of the cases and was nonischemic (degenerative, rheumatic, postendocarditis, or myxomatous) in 133 (77.77%) of the cases. The studied clinical parameters were age (mean, 59.34±11.74 years), sex (94 men, 54.97%), and functional preoperative NYHA class (II, 39.18%; III, 49.12%; IV, 11.69%).

The mean sPAP was 59.04±16.95 mm Hg, and the mean LVEF was 51.69%±13.15%. Before surgery, 60.82% of the patients belonged to NYHA class III or IV. The mean TAPSE was 18.51±4.77 mm.

Age did not influence the choice of type of surgery (*P* = .86), and women had a significantly higher number of replacement operations (*P* < .001), especially owing to a predominance of rheumatic pathology. The LVEF was considerably lower in patients who underwent mitral valve repair than in those who underwent mitral valve replacement (47.03%±14.94% versus 54.54%±13.15%; *P* < .001), possibly because mitral valve repair was preferred for most patients with an ischemic etiology.

Table 1. Clinical and Echocardiographic Parameters according to Mortality*

Parameter	Nonsurvivors (n = 4)	Survivors (n = 167)	*P*
Age, y	62.75 ± 17.92	58.73 ± 11.62	.5
Male sex, n	2 (50%)	92 (55.09%)	.96
Preoperative NYHA class IV, n	3 (75%)	17 (10.18%)	<.001
sPAP, mmHg	71.75 ± 5.06	58.73 ± 17.03	.13
LVEF, %	46.75 ± 12.2	51.81 ± 13.19	.45
PAT/PET	0.26 ± 0.04	0.38 ± 0.08	.04
EDRVD, mm	41.33 ± 6.11	36.09 ± 6.45	.16
Pericardial fluid, n	1 (25%)	3 (1.79%)	.71
Indexed right atrium area, mm/m^2	20.91 ± 4.3	13.78 ± 4.35	.002
TAPSE, mm	13.5 ± 7.4	18.69 ± 4.71	.03
Preoperative tricuspid regurgitation ≥ 3, n	2 (50%)	36 (21.55%)	.45
Concomitant CABG, n	3 (75%)	49 (29.34%)	.05
Tricuspid repair, n	1 (25%)	28 (16.76%)	.81
Prosthesis, n	2 (50%)	75 (44.91%)	.83

*Data are presented as the mean SD or as the number of patients. NYHA indicates New York Heart Association; sPAP, systolic pulmonary artery pressure; LVEF, left ventricular ejection fraction; PAT, pulmonary acceleration time; PET, pulmonary ejection time; EDRVD, end-diastolic right ventricular diameter; TAPSE, tricuspid annular plane systolic excursion; CABG, coronary artery bypass grafting.

The patients with ischemic mitral valve regurgitation were significantly older than the rest of the patients (63.64±7.44 years versus 57.41±12.4 years; *P* = .003) and had a considerably lower LVEF (47.35%±13.42% versus 52.96%±12.85%; *P* = .02). There were no significant differences with respect to the remaining clinical and echocardiographic characteristics.

Four patients included in the study died (ie, a 2.34% mortality rate). Table 1 shows the values for clinical and echocardiographic parameters according to the patients' vital status. The univariate analysis identified statistically significant differences in the risk for perioperative death for the following categories: preoperative NYHA class IV, PAT/PET ratio, TAPSE, the indexed area of the right atrium, and concomitant CABG surgery. In the multivariate analysis, the indexed right atrium area and concomitant CABG retained their statistical significance (Table 2).

Table 2. Multivariate Analysis for Mortality*

Independent Variable	Coefficient	Standard Error	*t*	*P*
Indexed right atrium area	0.01460	0.004118	3.546	<.001
Concomitant CABG	0.1051	0.04016	2.616	.0103

*CABG indicates coronary artery bypass grafting.

The secondary end point was a composite that included postoperative complications. We defined a first group with no postoperative complications and a second group of patients whose postoperative evolution was burdened by the following: renal, hepatic, pleural, or pericardial complications; prolonged mechanical ventilation and inotropic support; lengthy hospitalization in the intensive care unit; need for a new surgical procedure; use of pulmonary vasodilator drugs; or use of an intra-aortic balloon pump. The results are shown in Table 3. The univariate analysis revealed statistically significant differences for preoperative NYHA classes III and IV, sPAP, LVEF, PAT/PET ratio, right ventricular end-diastolic diameter, TAPSE, the indexed right atrium area, presence of pericardial fluid, preoperative tricuspid regurgitation >2, and need for concomitant tricuspid valve repair. The multivariate analysis (Table 4) revealed statistically significant echocardiographic parameters (the indexed right atrium area, LVEF, and presence of pericardial fluid) and clinical parameters (preoperative NYHA class), whereas from the point of view of the type of surgical procedure, concomitant CABG had statistically significant relevance.

Table 3. Clinical and Echocardiographic Parameters according to Operative Complications*

Parameter	Group 1 (No Complications, n = 117)	Group 2 (Complications, n = 54)	*P*
Age, y	58.27 ± 11.08	60.03 ± 13.16	.36
Male sex, n	63 (53.84%)	31	.738
Preoperative NYHA class, n			
II	62 (52.99%)	5 (9.26%)	<.001
III	51 (43.59%)	33 (61.11%)	
IV	4 (3.42%)	16 (29.63%)	
sPAP, mmHg	53.59 ± 15.07	70.83 ± 14.76	<.001
LVEF, %	53.26 ± 11.52	48.27 ± 15.72	.021
PAT/PET	0.39 ± 0.07	0.32 ± 0.09	.025
EDRVD, mm	34.78 ± 6.24	38.86 ± 6.09	<.001
Pericardial fluid, n	3 (2.56%)	10 (18.51%)	<.001
Indexed right atrium area, mm/m^2	12.71 ± 3.81	16.23 ± 4.73	<.001
TAPSE, mm	19.86 ± 4.17	16.14 ± 4.88	<.001
Preoperative tricuspid regurgitation ≥ 3, n	18 (15.38%)	20 (37.03%)	.03
Concomitant CABG, n	30 (25.64%)	22 (40.74%)	.046
Tricuspid repair, n	13 (11.11%)	16 (29.63%)	.005
Prosthesis, n	49 (41.88%)	28 (51.85%)	.22

*Data are presented as the mean SD or as the number of patients. Abbreviations are expanded in the footnote to Table 1.

Table 4. Multivariate Analysis for Complications*

Independent Variable	Coefficient	Standard Error	*t*	*P*
Indexed right atrium area	0.002714	0.01055	2.572	.0118
Concomitant CABG	0.2102	0.09038	2.326	.0223
Preoperative NYHA class	0.1803	0.06435	2.802	.0062
LVEF	-0.009312	0.003040	-3.064	.0029
Pericardial fluid	0.3258	0.1346	2.421	.0175

*Abbreviations are expanded in the footnote to Table 1.

To determine the influence of PH severity on the patients' immediate postoperative evolution, we used the respective ROC curves for sPAP and for mortality and immediate postoperative complications. An sPAP value >65 mm Hg showed the highest possible specificity and sensitivity for risk of perioperative mortality for patients with mitral regurgitation (area under the ROC curve [AUC], 0.782; $P < .001$) (Figure 1), whereas for the secondary end point, an sPAP value of 60 mm Hg had the highest sensitivity and specificity (AUC, 0.82; $P < .001$) (Figure 2).

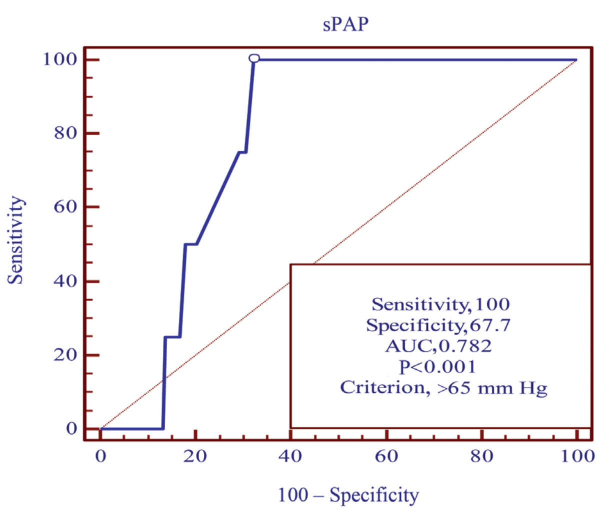

Figure. 1. Receiver operating characteristic (ROC) curve for systolic pulmonary artery pressure (sPAP) and mortality. AUC indicates area under the ROC curve.

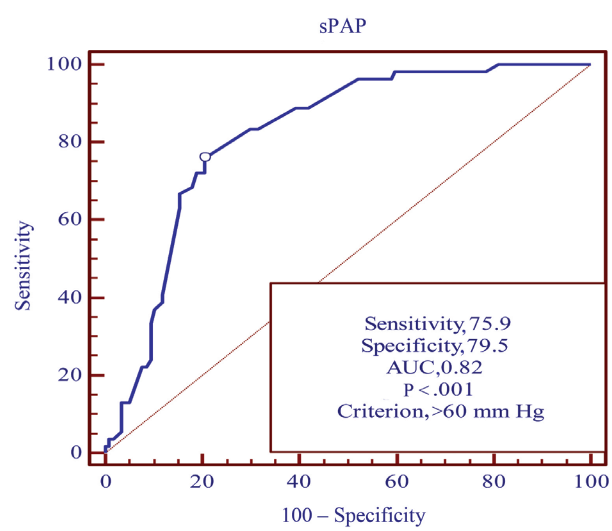

Figure 2. Receiver operating characteristic (ROC) curve for systolic pulmonary artery pressure (sPAP) and perioperative complications. AUC indicates area under the ROC curve.

Table 5. Influence of Severe Pulmonary Hypertension on Mortality and Complications*

	General Group (n = 171)			Preserved LVEF (n = 72)		
Parameter	sPAP < 60 mmHg (n = 106)	sPAP > 60 mmHg (n = 65)	*P*	sPAP < 60 mmHg (n = 43)	sPAP > 60 mmHg (n = 29)	*P*
Death, n	0	4	.039	0	1	.22
Mechanical ventilation > 24h, n	2	20	<.001	0	7	<.001
Renal complications, n	2	7	.029	0	4	.01
Liver complications, n	4	12	.003	2	7	.01
Pericardial complications, n	2	12	<.001	0	6	.002
Pleural complications, n	6	4	.839	2	3	.98
Reintervention, n	0	3	.102	0	2	.08
IABP, n	0	2	.278	0	0	–
ERA/prostanoids/PDE5I, n	2	9	.005	0	3	.03
Hospitalization in ICU, d	6.57 ± 2.01	10.41 ± 4.39	<.001	6.12 ± 1.75	9.36 ± 3.93	<.001
Need for inotropic support, d	4.06 ± 2.42	7.86 ± 4.44	<.001	3.36 ± 2.41	6.78 ± 3.68	<.001

*Data are presented as the mean SD or as the number of patients. LVEF indicates left ventricular ejection fraction; sPAP, systolic pulmonary artery pressure; IABP, intra-aortic balloon pump; ERA, endothelin receptor antagonist; PDE5I, phosphodiesterase-5 inhibitor; ICU, intensive care unit.

We defined severe PH as an sPAP value >60 mm Hg and analyzed its impact on risks of mortality and perioperative complications in patients with mitral valve regurgitation. The results of this analysis are presented in Table 5. Severe PH is associated with a significant increase in the mortality rate, longer hospitalization in the intensive care unit, mechanical ventilation >24 hours, longer inotropic support, and renal, hepatic, and pericardial complications, as well as use of ERAs, PDE5Is, and prostanoids. To minimize the influence of the LVEF on postoperative evolution, we selected a subgroup of patients with a preserved LVEF (>60%) and analyzed the impact of severe PH on the same parameters (Table 5). We concluded that severe PH also occurs in patients with a normal systolic LV function and that their postoperative evolution is burdened by numerous complications.

DISCUSSION

The detection of the best time of operation for patients with mitral valve regurgitation is still a controversial topic. PH frequently occurs in patients with chronic mitral regurgitation, even when their systolic LV function is normal. The absence of extensive studies assessing the impact of PH on the evolution of mitral regurgitation patients is demonstrated by the recommendation class (IIa) and by the C level of evidence in both the ESC and ACC/AHA guidelines for the management of valvular diseases [Bonow 2006; Vahanian 2007]. Although surgery is traditionally recommended when sPAP values are >50 mm Hg, our research shows that severe PH (sPAP >60 mm Hg) is associated with high operative mortality rates and considerable renal, hepatic, and pericardial complications, which extend the patient's hospitalization in the intensive care unit, require longer mechanical ventilation times, require longer periods of inotropic support, and require the use of pulmonary vasodilator drugs (ERAs, PDE5Is, and prostanoids). All of these measures significantly increase the patient's operative risks and surgery costs. Other researchers have also shown that severe preoperative PH is an important predictor of adverse cardiac events (defined as cardiac death, readmission for heart failure, and fatal arrhythmia) [Kainuma 2011], operative mortality [Le Tourneau 2010; Ghoreishi 2011], and late-survival rates [Ghoreishi 2011]—both in patients with organic mitral valve regurgitation and in those with functional mitral regurgitation. We conclude from our research that surgery is advisable in the early stages after PH onset to minimize surgery-related risks, as other investigators have shown in recent studies [Kang 2009; Montant 2009; Rosenhek 2010; Ghoreishi 2011]. The detection of exercise-induced PH is reasonable for asymptomatic patients [Magne 2010], because it predicts symptom occurrence and represents an indication for operation in these patients, according to the ACC/AHA guidelines [Bonow 2006].

The patients' age and sex had no influence on their postoperative progress. The preoperative NYHA class proved both an important predictor of postoperative mortality (in the univariate analysis) and a predictor of the occurrence of immediate complications (in both univariate and multivariate analyses). This finding supports the indication of early surgery after the onset of symptoms.

Among the echocardiographic parameters analyzed with regard to the primary end point (mortality), the univariate analysis enabled us to identify statistical significance for the PAT/PET ratio (a marker of PH severity), the indexed right atrium area, and TAPSE. These results indicate that the occurrence of systolic right ventricular dysfunction in PH patients is associated with a poor prognosis. In other research, a TAPSE value 12 mm [Di Mauro 2007] or 14 mm [Dini 2007] has also been associated with a major negative prognosis for mitral regurgitation. In our study, the LVEF was not significantly associated with mortality, suggesting that the onset of right ventricle dysfunction plays a more important role in patients with mitral regurgitation and PH.

The only echocardiographic predictor of mortality in the multivariate analysis was the indexed right atrium area. Right atrium dilation is due to higher pressure in the right atrium, which is due to tricuspid regurgitation and/or a high end-diastolic right ventricle pressure. The right atrial size as measured by echocardiography has been shown to be strongly correlated with invasive parameters of right ventricular diastolic filling and to predict a high end-diastolic right ventricle pressure [Do 2011]. Although less studied than the left atrium in patients with mitral regurgitation, a dilated right atrium is a simple, quantitative, and reproducible echocardiographic marker of the onset of right ventricle failure. Right atrium dilation was initially associated with a poor prognosis in patients with idiopathic pulmonary artery hypertension [Raymond 2002] and later in patients with systolic heart failure [Sallach 2009].

Several echocardiographic parameters have been associated with a complicated postoperative evolution. These parameters may be divided into markers of systolic LV dysfunction (LVEF), markers of severe PH (sPAP, PAT/PET), and markers of right ventricle dysfunction (TAPSE, right cavity dilation, tricuspid regurgitation severity). Systolic LV dysfunction is a well-known negative prognostic factor in patients with mitral regurgitation [Bonow 2008]; however, the impact of PH and right ventricle dysfunction has been less studied.

In the multivariate analysis, the low LVEF, the presence of pericardial fluid, and the indexed right atrium area remained significantly associated with postoperative complications. The presence of pericardial fluid is a well-known negative prognostic factor in PH; it is also a sign of right ventricle dysfunction. Such pericardial fluid is a consequence of dysfunctions in the venous and lymphatic drainage toward the right atrium due to the latter's high pressure [Raymond 2002]. A recent meta-analysis that addressed prognostic factors in idiopathic pulmonary artery hypertension found the pericardial fluid to be the only reproducible echocardiographic predictor of mortality [Swiston 2010]. In addition, the presence of pericardial fluid was the only echocardiographic mortality-associated parameter shown in the REVEAL registry for pulmonary artery hypertension [Benza 2010].

Concomitant CABG surgery was accompanied by higher rates of mortality and postoperative complications, in both the univariate and multivariate analyses. As we have already shown, this finding largely is because the patients with ischemic mitral regurgitation were considerably older and had lower ejection fractions and because an ischemic etiology is generally associated with a poorer prognosis. Previous studies have also shown that associated significant coronary lesions in patients with mitral regurgitation have a negative influence on their prognosis, even in patients with different etiologies [Gillinov 2005; Sirivella 2007].

Study Limitations

Our research relies on retrospectively collected data, which enabled us to define a particular risk profile, both clinically and echocardiographically. It would be interesting to assess many different echocardiographic parameters to determine the impact of PH on the prognosis of patients with mitral valve regurgitation (tissue Doppler of the tricuspid ring and other methods for assessing right ventricle function). Our research included only symptomatic patients with PH at rest. Larger studies are needed to evaluate the prognostic importance of exercise-induced PH in asymptomatic patients. Our research included patients with different mitral regurgitation etiologies. Further detailed analyses of each of these subsets of patients are necessary.

CONCLUSIONS

PH is a strong short-term negative prognostic factor for patients with mitral regurgitation who are to undergo mitral valve surgery. Surgical procedures should be performed in the early stages after PH onset. Echocardiographic examination has useful, simple, and reproducible tools for classifying operative risks. An ischemic etiology and the need for concomitant CABG surgery are additional risk factors in patients with mitral regurgitation and PH.

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