A contemporary analysis of pulmonary hypertension in patients undergoing mitral valve surgery: Is this a risk factor?

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ABSTRACT

Objective: Pulmonary hypertension (PHT) has been considered a risk factor for mortality in cardiac surgery. Among mitral valve surgery (MVS) patients, we sought to determine if severe PHT increases mortality risk and if patients who undergo concomitant tricuspid valve surgery (TVS) incur additional risk.

Methods: Preoperative PHT was assessed in 1571 patients undergoing MVS, from 2004 to 2013. Patients were stratified into PHT groups as follows (mm Hg): none (<35); moderate (35-49); severe (50-79); and extreme (≥80). Propensity-score matching resulted in a total of 430 patients, by PHT groups, and 384 patients, by TVS groups.

Results: Patients with severe PHT had higher mortality, both 30-day (4% PHT vs 1% no PHT, $P < .02$) and late (defined as survival at 5 years): 75.5% severe versus 91.9% no PHT ($P < .001$). In propensity-score-matched groups, severe PHT was not a risk factor for 30-day (3% each, $P = 1.0$) or late mortality (86.2% severe vs 87.1% no PHT; $P = .87$). TVS did not increase 30-day (4.7% TVS vs 4.2% no TVS, $P = .8$) or late mortality (78.7% TVS vs 75.3% no TVS, $P = .90$). Late survival was lower in extreme PHT (75.4% vs no PHT 91.5%, $P = .007$), and a trend was found in 30-day mortality (11% extreme vs 3% no PHT, $P = .16$).

Conclusions: Mortality in MVS is unaffected by severe PHT or the addition of TVS, yet extreme PHT remains a risk factor. Severe PHT (50-79 mm Hg) should not preclude surgery; concomitant TVS does not increase mortality. (J Thorac Cardiovasc Surg 2016;151:1288-99)

Kaplan-Meier estimates in propensity-score matched groups: severe group (Severe) versus no PHT (No).

Central Message

Mortality in mitral valve surgery is unaffected by severe pulmonary hypertension or the addition of tricuspid valve surgery, but extreme pulmonary hypertension remains a risk factor.

Perspective

Pulmonary hypertension is considered a risk factor for 30-day mortality in MVS patients. Our study found no difference in mortality for MVS patients with severe PHT or with the addition of TVS. Severe PHT should not be a contraindication to MVS, and TVS can be safely added; however, extreme PHT remains a consideration when determining operative risk.

See Editorial Commentary page 1300.

Pulmonary hypertension (PHT) historically has been considered a mortality risk factor in cardiac surgical patients, and is found in 15% to 60% of patients who have valvular heart disease. PHT is associated with a

higher risk of cardiovascular events with medical management, during valve surgery, and even after successful surgical intervention.¹ In patients who have mitral valve disease, PHT is a common finding in the preoperative evaluation,² often resulting from elevated left atrial pressures that lead to pulmonary vascular remodeling.³ Longstanding PHT increases the afterload on the right ventricle, leading to hypertrophy and eventually, cor pulmonale.³ This right-heart

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Abbreviations and Acronyms

MVS	= mitral valve surgery
PASP	= pulmonary artery systolic pressure
PHT	= pulmonary hypertension
RHC	= right-heart catheterization
STS	= Society of Thoracic Surgeons
TVS	= tricuspid valve surgery

failure is associated with tricuspid annulus, right ventricular dilation, and tricuspid regurgitation, further exacerbating right ventricular dysfunction.^{4,5} Current guidelines suggest that the most effective therapy for severe degenerative mitral regurgitation is surgical intervention,⁶ yet in some cases, operative treatment is not pursued, owing to perceived high perioperative risks.

In this study, we aim to elucidate the isolated impact of PHT on short- and long-term outcomes of patients who have PHT. Although conventions vary, we defined PHT as the presence of a pulmonary artery systolic pressure (PASP) >35 mm Hg, which we have further stratified into moderate (35-49 mm Hg), severe (50-79 mm Hg), and extreme (≥ 80 mm Hg). Preoperatively, PASP is either measured directly via right-heart catheterization (RHC), or estimated via Doppler echocardiography, using the simplified Bernoulli equation.^{7,8}

Up to 50% of patients undergoing MVS have tricuspid valve regurgitation,^{9,10} which has been shown to negatively affect survival independently.¹¹ Current guidelines provide a Class I indication for repair of severe tricuspid regurgitation for patients undergoing left-sided valve surgery,⁶ consistent with long-term outcomes demonstrating a survival advantage of tricuspid valve repair concomitant with MVS.^{10,12-14} We performed a subset analysis on the MVS patients who had PHT, to assess the impact of concomitant tricuspid valve surgery (TVS) on patient outcomes.

METHODS

Patients and Study Design

Data for this project were obtained from the Cardiovascular Research Database in the Clinical Trial Unit of the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital. This database was approved by the Institutional Review Board at Northwestern University. Any subjects who declined to participate in the project were not included in the analysis. Between April 1, 2004, and December 31, 2013, a total of 3755 adult patients underwent first-time valve surgery, excluding patients who had transcatheter aortic valve replacement, ventricular assist devices, transplant, trauma, or endocarditis. Of these, 1714 patients had MVS. Preoperative PASP data were available in 1571 (92%) cases: 1075 (62.7%) patients had PHT (defined as PASP >35 mm Hg); 496 (28.9%) patients had no PHT; and 143 (8.34%) patients had unknown PASP values. PHT patients were further stratified into groups based on PASP (mm Hg): 600 (55.8%) moderate (35-49); 426 (39.6%) severe (50-79); and 49 (4.6%) extreme (≥ 80).

Our institutional database did not indicate whether the PASP was obtained by echocardiography or RHC. In patients who did not receive an RHC study preoperatively, PASP values were obtained from Doppler echocardiography, using the modified Bernoulli equation ($4 \times [\text{tricuspid regurgitation}]^2 + \text{right atrial pressure}$).¹⁵ The absence of pulmonary stenosis and right ventricular outflow obstruction allowed for the estimation of PASP from the right ventricular systolic pressures obtained from echocardiography. When both RHC and echocardiography were obtained preoperatively, results obtained from RHC were used preferentially. No intraoperative echocardiogram measurements were used. Baseline PASP data were not available on 143 patients, who were excluded from this study.

Mortality Data Collection

Mortality data were aggregated continuously and in an equally thorough manner by a dedicated team of research personnel upon consulting various sources, including the following: (1) the local cardiovascular research database registry, which captures extensive information via postal surveys mailed (to patients alive at discharge) at 6 and 12 months after surgery, and annually thereafter or until notice of death; (2) copies of records for medical procedures and hospitalizations, to verify patient self-reported events captured via survey questionnaires; (3) reviews of external medical records and written or electronic correspondence with the referring or treating physician; (4) direct interviews with the patient during follow-up visits and clinical evaluation; (5) online death indexes, including the Social Security Death Index and genealogy resources (eg, ancestry.com) that provide copies of the death information, for this index, that is supplied directly by family members (at least once a year, our dedicated team reviews the entire cohort of patients known to be alive at last follow-up); and (6) local newspaper death notices, because a substantial segment of our patient population resides in the metropolitan Chicago area or in a state neighboring Illinois. Utilizing these sources, follow-up information was available on 100% of the cohort. The Society of Thoracic Surgeons (STS) database definitions were used for 30-day mortality.

Statistical Analysis

Given the risk for confounding due to baseline imbalances, we employed propensity-score matching methods. Groups compared were matched 1-to-1, based on this score, using a greedy algorithm with a caliper of size 0.2 logit propensity-score standard deviation units. The adequacy of between-groups balance in each baseline characteristic used to create the propensity-score model was assessed using standardized differences¹⁶ (orange color for the prematching groups; violet color for the matched groups). Variables used in the matching process were as follows: age; gender; body surface area; preoperative creatinine level; Ambler score; angina; coronary artery disease; family history of coronary artery disease; diabetes; hypercholesterolemia; hypertension; chronic obstructive pulmonary disease; cerebrovascular accident; prior coronary artery bypass graft; prior valve surgery; repeat sternotomy; prior myocardial infarction; New York Heart Association functional class III or IV; history of atrial fibrillation; elective status; and mitral valve functional class and TVS (except for the subgroup analysis comparing concomitant TVS vs no TVS among MVS patients).

Additional propensity-score matched analyses have compared the incidence of receiving a predischarge permanent pacemaker by concomitant tricuspid valve repair or replacement status, among the subgroup of patients with preoperative PHT, and separately in the entire cohort (PHT classification was included as a variable in the respective propensity-score models). Propensity-score matching was implemented using the SAS macro %GMATCH (SAS Institute, Inc, Cary, NC).

Kaplan-Meier curves with corresponding 95% pointwise confidence intervals were used to summarize postoperative overall survival; group comparisons were based on the log-rank test. The association between long-term mortality and PASP as a continuous variable was assessed using

TABLE 1. Patient characteristics by PHT classification, preoperatively

Variable	None (n = 496)	PHT (mm Hg)			P value
		Moderate (35-49) (n = 600)	Severe (50-79) (n = 426)	Extreme (≥ 80) (n = 49)	
Age (y), mean $\pm$ SD	59.4 $\pm$ 13.9	65 $\pm$ 12.9	68 $\pm$ 12.1	65.7 $\pm$ 13.1	<.001
LV ejection fraction %	60 (53, 65)	57 (45, 61.5)	55 (43, 63)	60 (53, 65)	<.001
Female gender	202 (41)	279 (47)	213 (50)	29 (59)	.008
Diabetes	48 (10)	76 (13)	95 (22)	12 (24)	<.001
Hypertension	262 (53)	354 (59)	282 (66)	32 (65)	<.001
Chronic lung disease	48 (10)	86 (14)	74 (17)	10 (20)	.004
Cerebrovascular disease	40 (8)	63 (11)	62 (15)	5 (10)	.017
Prior stroke	22 (4)	36 (6)	33 (8)	5 (10)	.12
Previous MI	48 (10)	78 (13)	70 (16)	7 (14)	.025
Prior pacemaker	22 (4)	38 (6)	46 (11)	5 (10)	.001
Congestive heart failure	137 (28)	246 (41)	241 (57)	30 (61)	<.001
Mitral stenosis					<.001
Yes	33 (6.5)	81 (13.5)	110 (26)	20 (41)	
No	430 (87)	471 (78.5)	275 (64)	24 (49)	
Missing	33 (6.5)	48 (8)	41 (10)	5 (10)	
NYHA functional class					<.001
I	157 (32)	128 (21)	60 (14)	2 (4)	
II	219 (44)	234 (39)	127 (30)	14 (29)	
III	95 (19)	184 (31)	188 (44)	24 (49)	
IV	17 (3)	49 (8)	48 (11)	8 (16)	
Missing	8 (1)	5 (1)	3 (1)	1 (2)	
Coronary artery disease					<.001
Yes	136 (27)	223 (37)	192 (45)	23 (47)	
No	346 (70)	374 (62.5)	230 (54)	26 (53)	
Missing	14 (3)	3 (0.5)	4 (1)	0 (0)	

Values are n (%), unless otherwise indicated. PHT, Pulmonary hypertension; SD, standard deviation; LV, left ventricular; MI, myocardial infarction; NYHA, New York Heart Association.

unadjusted and covariate-adjusted Cox regression models, with a smoothing spline effect for PASP,¹⁷ using the R package *smoothHR* (cran.r-project.org/package=smoothHR). Variables included in the adjusted model were determined using stepwise selection in a separate Cox regression model; the initial pool of variables consisted of those factors used to create the propensity-score model described earlier. To ensure internal mortality data consistency, we have compared overall survival Kaplan-Meier estimates, by surgery year in the entire cohort, and separately within each pulmonary hypertension severity degree.

Means $\pm$ standard deviations or medians (first quartile, third quartile) were used to summarize continuously distributed variables; the 2-sample unequal variance *t* test or the Wilcoxon rank-sum test were used to compare groups. Counts and percentages were used to summarize variables that had discrete distributions; χ^2 analysis, Kruskal-Wallis analysis of variance, or Fisher exact tests were used to compare groups. Baseline and follow-up PASP data were compared using the paired *t* test. Tests were 2-sided, without multiplicity adjustments. Statistical analyses were performed using SAS, version 9.3 software (SAS Institute, Inc, Cary, NC), R v. 3.2.1 (www.R-project.org), and RStudio (www.rstudio.com).

RESULTS

Prematching Groups

The PHT patients were older and presented with more comorbidities, including prior myocardial infarction, coronary artery disease, cerebrovascular disease, diabetes, congestive heart failure, chronic lung disease, and higher New York Heart Association functional class. Overall,

392 (25% of 1571) patients had concomitant TVS (3.6% replacement; 96.4% repair). In addition, 244 of the 1571 MVS patients had mitral stenosis, with the highest proportion in the extreme PHT group (20 of 49 [40.8%]) (Table 1).

After Propensity-Score Matching

The patients who had PHT had a longer perfusion and crossclamp time, along with more concomitant procedures, including coronary artery bypass grafting, aortic valve surgery, and TVS (Table 2). Mitral valve repair rates were higher among patients who did not have PHT. Those who did have PHT additionally had a longer postoperative length of stay, higher 30-day readmission rates, higher 30-day mortality, and lower long-term overall survival (Figure 1; $P < .001$).

Severe versus no PHT. Propensity-score matching resulted in 215 pairs of patients with severe PHT versus no PHT, with adequate baseline covariate balancing (Figure 2, A). Thirty-day mortality (3% in each group, $P = 1.0$) and 5-year overall survival ($P = .87$; Figure 2, B; 5-year survival: 86.2% severe PHT vs 87.1% no PHT) were not significantly different. Postoperative hospital length of stay was similar (median 7 days, $P = .36$), as

TABLE 2. Intraoperative characteristics and postoperative outcomes, by preoperative PHT classification

Variable	None (n = 496)	PHT			P value
		Moderate (35-49) (n = 600)	Severe (50-79) (n = 426)	Extreme (≥80) (n = 49)	
Perfusion time (min)	97 (77, 129)	117 (88, 151.5)	128.5 (103, 162)	140 (116, 182)	<.001
Crossclamp time (min)	80 (66, 105)	91 (69, 120)	93 (73, 121)	107 (85, 141)	<.001
Coronary artery bypass graft	118 (24)	178 (30)	139 (33)	16 (33)	.021
Aortic valve surgery	73 (15)	135 (23)	118 (28)	17 (35)	<.001
Tricuspid valve surgery	42 (8)	138 (23)	189 (44)	23 (47)	<.001
Mitral valve surgery type					<.001
Repair	421 (85)	432 (72)	239 (56)	17 (35)	
Replacement	75 (15)	168 (28)	187 (44)	32 (65)	
Postoperative length of stay (d)	6 (4, 7)	7 (5, 9)	8 (6, 10)	9 (6, 14)	<.001
Readmission within 30 days	52 (10.5)	69 (11.5)	72 (16.9)	8 (16.3)	.008
30-d mortality (%)	6 (1.2)	17 (2.8)	16 (3.8)	6 (12)	<.001

Values are n (%), unless otherwise indicated. PHT, Pulmonary hypertension.

were 30-day readmission rates (17% severe vs 15% no PHT, $P = .7$). Similarly, no difference was found in outcomes for moderate versus no PHT.

Extreme versus no PHT. In a comparison of extreme PHT versus no PHT, propensity-score matching yielded a total of 37 pairs, showing adequate baseline covariate balancing (Figure 3, A). Long-term overall survival was significantly lower among patients who had extreme PHT ($P = .007$; Figure 3, B; 5-year survival: 75.4% extreme PHT vs 91.5% no PHT). A trend toward higher 30-day mortality has been observed for patients with extreme PHT (11% vs 3%, $P = .16$).

Subgroup Analysis Among PHT Patients: Comparison by Concomitant TVS Status

In the original groups, patients that underwent concomitant TVS were older (69.3 ± 11.8 vs 64.7 ± 12.8 years, $P < .001$), had a higher median PASP (54 vs 45 mm Hg, $P < .001$), and a higher percentage of those in New York Heart Association functional class III or IV (55% vs 43%, $P < .001$) than did the patients who did not have TVS. Postoperatively, patients who underwent TVS had a longer length of stay (8 vs 7 days, $P < .001$) and had lower

long-term overall survival than those with no TVS (5-year survival of 73.7% vs 84.9%, respectively, $P < .001$).

Propensity-score matching yielded 192 pairs of concomitant TVS versus no-TVS patients, with adequate baseline covariate balancing (Figure 4, A). We found no differences in 30-day mortality (5% for TVS vs 4% for no TVS, $P = .8$) or 5-year overall survival ($P = .90$, 5-year survival: 78.7% TVS vs 75.3% no TVS) (Figure 4, B).

Baseline Pulmonary Artery Systolic Pressure as a Continuous Variable

An exact baseline PASP was available for 1327 of the 1571 study participants. The association between PASP and long-term all-cause mortality in unadjusted and covariate-adjusted (Figure 5, A and B) models shows that the effect of baseline PASP is nonlinear, and that increased PASP is associated with increased mortality, thus confirming and further refining the unadjusted results (Figure 1). After adjusting for age, Ambler score, creatinine level, chronic obstructive pulmonary disease, and New York Heart Association functional class III or IV, PASP was not a significant risk factor for mortality, except in its high ranges (Figure 5, B). This finding provides further support to our propensity-score matched analyses, which showed that extreme, but not severe or moderate, PHT is associated with increased all-cause mortality. An additional analysis (not shown), adjusting for all the variables included in the propensity-score model, produced results virtually identical to those in Figure 5, B. Internal mortality data consistency checks have revealed that overall Kaplan-Meier survival estimates were not different by surgery year in the entire cohort, or separately within each PHT severity-degree group.

Postsurgical Follow-up

Among all patients, the mean PASP decreased, from 45.8 ± 14.6 to 35.2 ± 13.1 mm Hg ($P < .001$), with

FIGURE 1. Kaplan-Meier survival estimates by pulmonary hypertension (PHT) classification (none, moderate, severe, extreme).

FIGURE 2. Standardized differences in: (A) baseline covariates; and (B) Kaplan-Meier survival estimates in PS-matched analyses for severe versus no PHT. *PS*, Propensity score; *Hx*, history; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *Afib*, atrial fibrillation; *MV*, mitral valve; *SAM*, systolic anterior motion.

follow-up in 484 (31%) patients during a median of 2 years. The change in the individual PHT groups was as follows (mm Hg): extreme ($n = 13$): 89.9 ± 10.5 to 51.5 ± 16.1 ; severe ($n = 161$): 59.2 ± 7.1 to 39.2 ± 14.5 ; and moderate ($n = 220$): 40.8 ± 4.5 to 34 ± 11.4 ; all $P < .001$. For the no-PHT group ($n = 90$), the decrease was from 28.1 ± 4.1 to 28.4 ± 9.2 mm Hg ($P = .7$).

Incidence of Predischarge Permanent Pacemaker Implantation in Association With Concomitant TVS

Entire cohort. Patients who underwent concomitant tricuspid valve repair or replacement, compared with those that did not, had a significantly higher incidence of permanent pacemaker implantation prior to discharge (before matching: 12.0% vs 4.6%, $P = .001$; propensity-score matching: 12.4% vs 6.0%, $P = .031$). After excluding discharge deaths and patients that had a

permanent pacemaker preoperatively, similar results were observed (before matching: 14.0% vs 4.9%, $P = .001$; propensity-score matching: 15.2% vs 7.9%, $P = .038$).

In a comparison of concomitant TVS (repair) versus no TVS, the incidence of permanent pacemaker implantation prior to discharge was significantly different in the before-matching groups (11.4% vs 4.6%, $P = .001$), but not in the propensity-score matching groups (10.1% vs 6.7%, $P = .12$). However, after further excluding discharge deaths and those patients that had a permanent pacemaker preoperatively, a higher incidence was observed among concomitant TVS (repair) patients before (13.7% vs 4.9%, $P = .001$), compared with after (13.0% vs 7.6%, $P = .044$), matching (Table 3).

PHT patient subgroup. Patients with PHT undergoing concomitant TVS for repair or replacement had a significantly higher incidence of permanent pacemaker

FIGURE 3. Standardized differences in: (A) baseline covariates; and (B) Kaplan-Meier survival estimates in propensity score–matched analyses for extreme versus no PHT. *PS*, Propensity score; *Hx*, history; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *Afib*, atrial fibrillation; *MV*, mitral valve; *SAM*, systolic anterior motion.

implantation prior to discharge, compared with those that did not undergo concomitant TVS, before matching (11.7% vs 6.1%, $P = .001$), but not propensity-score matching (10.3% vs 6.7%, $P = .13$). After excluding discharge deaths, and patients who had a permanent pacemaker preoperatively, concomitant TVS for repair or replacement was associated with a higher incidence of permanent pacemaker implantation before discharge, in the original groups (13.6% vs 6.6%, $P = .001$), compared with the propensity-score matched groups (13.2% vs 6.8%, $P = .021$).

For concomitant TVS for repair, versus no TVS, the incidence of pacemaker implantation before discharge was significantly different in the groups before matching

(11.2% vs 6.1%, respectively, $P = .003$), but not in the propensity-score matched groups (10.2% vs 7.1%, $P = .18$). After excluding discharge deaths and preoperative permanent pacemaker cases, a higher incidence was observed among concomitant TVS for repair patients (13.5% vs 6.6%, $P = .001$) in the groups before matching, but only a trend was observed propensity-score matching (12.4% vs 7.7%, respectively, $P = .09$).

DISCUSSION

Propensity-score matched continuous variable, and multivariable analysis, of patients who underwent MVS indicates that severe PHT is not a significant risk factor for short- or long-term unfavorable outcomes. Multiple

FIGURE 4. Standardized differences in: (A) baseline covariates; and (B) Kaplan-Meier survival estimates in PS-matched analyses by concurrent TVS status in patients with PHT undergoing MVS. *PS*, Propensity score; *Hx*, history; *CAD*, coronary artery disease; *CABG*, coronary artery bypass graft; *MI*, myocardial infarction; *NYHA*, New York Heart Association; *Afib*, atrial fibrillation; *TVS*, tricuspid valve surgery.

prior studies have grouped patients who have PASP >50 mm Hg. By separately stratifying patients in the extreme PASP group with those who have PASP >80 mm Hg, we have observed comparable outcomes between patients who have severe PHT and those without evidence of PHT. These results suggest that the degree of PHT may be an important consideration when calculating risk for postoperative mortality. Perhaps PHT should only raise

reluctance to operate when it is extremely elevated (>80 mm Hg), or alternative percutaneous approaches should be pursued.¹⁸

Prior studies have suggested that PHT adversely affects short- and long-term survival in patients who undergo MVS.¹⁹⁻²¹ The 30-day mortality risk effect of PHT has been included in the EuroSCORE (European System for Cardiac Operative Risk Evaluation) II model (which

FIGURE 5. Smooth hazard rate estimates for baseline pulmonary artery systolic pressure (as a continuous variable) and corresponding 95% confidence intervals in (A) unadjusted and (B) covariate-adjusted models. A baseline pulmonary artery systolic pressure value of 10 mm Hg serves as the reference point. *COPD*, Chronic obstructive pulmonary disorder; *NYHA*, New York Heart Association.

defines PHT as $PASP > 30$ mm Hg).²² The presence of PHT is collected as part of the STS database, but it has not been identified as a mortality risk factor in the STS risk score.²³ Recent series suggest that PHT should be included in the STS risk score.²⁴ However, in multivariate analyses, potential confounders (eg, chronic obstructive pulmonary disorder) in PHT patients undergoing MVS may have exaggerated the mortality risk.²⁵ Propensity-score matching can be used to reduce selection bias in nonrandomized trials.²⁶⁻²⁸

Additionally, recent publications have demonstrated increased PHT to be an independent risk factor in both coronary artery bypass grafting and aortic valve replacement. Kennedy and colleagues²⁴ reviewed more than 3000 cardiac surgical patients, finding that PHT was significantly associated with increased morbidity and mortality, even after accounting for STS risk. However, mitral operations made up a minor part of their group (6.9%), whereas most were coronary artery bypass grafting (67.5%) and aortic valve replacement (24.9%). Our study focused on MVS exclusively, although 909 of 1571 (57.9%) patients

underwent concomitant revascularization or another valvular procedure. In 2385 patients undergoing primary aortic valve replacement at the Cleveland Clinic, PHT was associated with worse early and late outcomes. In addition, post-aortic valve replacement right ventricular systolic pressure improvement was not stable, and it returned to preoperative levels after 3 to 4 years.²⁹ These outcomes suggested that earlier intervention for aortic stenosis could improve outcomes.

As for mitral valve replacement, Ghoreishi and colleagues¹⁹ reported on the impact of preoperative PHT (defined as $PASP \geq 40$ mm Hg) in surgical patients who had mitral regurgitation ($n = 888$). Most of their patients underwent RHC (68%). Using multivariate analysis, they concluded that preoperative $PASP$ was a predictor of late death (odds ratio: 1.018 per 1 mm Hg increase; 95% confidence interval: 1.007-1.028; $P = .001$). Their analysis yielded a hospital mortality of 12% in the severe group ($PASP > 60$ mm Hg), similar to our mortality result of 6 of 49 (12%) in the extreme group (> 80 mm Hg). They concluded that referral for MVS should be considered for

TABLE 3. Incidence of predischarge permanent pacemaker implantation, by concomitant TVS status

Comparison	Exclusions	Groups					
		Before matching			After propensity-score matching		
		Size (n)	Pacemaker (%)	P value	Size (n)	Pacemaker (%)	P value
Entire cohort*	No	392 vs 1179	12.0 vs 4.6	.001	186 vs 186	12.4 vs 6.0	.031
	Yes	321 vs 1103	14.0 vs 4.9	.001	164 vs 164	15.2 vs 7.9	.038
Entire cohort†	No	378 vs 1179	11.4 vs 4.6	.001	327 vs 327	10.1 vs 6.7	.12
	Yes	315 vs 1103	13.7 vs 4.9	.001	262 vs 262	13.0 vs 7.6	.044
PHT patients*	No	350 vs 725	11.7 vs 6.1	.001	282 vs 282	10.3 vs 6.7	.13
	Yes	286 vs 668	13.6 vs 6.6	.001	235 vs 235	13.2 vs 6.8	.021
PHT patients†	No	339 vs 725	11.2 vs 6.1	.003	283 vs 283	10.2 vs 7.1	.18
	Yes	281 vs 668	13.5 vs 6.6	.001	233 vs 233	12.4 vs 7.7	.09

Values are for TVS (*repair or replacement) or (†repair only) versus no TVS. Exclusions were discharge deaths and preoperative permanent pacemaker implantation. Analyses were performed separately in the entire cohort versus in the subgroup of patients who had preoperative PHT. PHT, Pulmonary hypertension.

patients who have PASP ≥ 40 mm Hg, given the increased surgical risk.

In contrast, our data suggest that surgery can be performed without increased risk from PHT as an independent factor, up to PASP of 80 mm Hg. Analysis of PASP and a continuous variable indicates that its effect on mortality is not linear and is statistically significant only toward the high end of the spectrum (Figure 5). In contrast, Ghoreishi and colleagues¹⁹ have assumed a *constant* PASP effect; hence, the inference can be drawn that a PASP increase from 30 to 40 mm Hg has the same effect on mortality as an increase from 80 to 90 mm Hg. Therefore, their model leads to an averaged PASP effect, but does not capture the differential PASP effect across its entire spectrum.

Tricuspid regurgitation may confound comparisons of patients who undergo MVS and have PHT. Our subgroup analysis of such patients demonstrated no significant differences in short- or long-term mortality, by concomitant TVS status. Our results suggest that when performing MVS on patients who have comorbid tricuspid regurgitation, TVS can be added without additional mortality risk. However, concomitant TVS (repair or replacement) was associated with a higher incidence of permanent pacemaker implantation prior to discharge, compared with no TVS, in both the before-matching and propensity-score matching groups.

Limitations

Our analysis has several limitations. PASP was obtained using both RHC and echocardiography, without recording the method in our database. For patients who have suspected PHT, however, RHC was often collected. Thus, RHC PASP measurements, considered the gold standard³⁰ in accurately measuring pulmonary artery pressures, were more often obtained in the severe- and extreme-risk groups. In addition, even with propensity-score matching,

unmeasured characteristics and confounders may be present.³¹ Our results refer to MVS patients specifically, and are thus not applicable to general cardiac surgical patients (for coronary artery bypass grafting, aortic valve surgery, etc). Despite our best efforts, maintaining the most up-to-date mortality status for each patient continues to be challenging. However, our multilayered and inclusive assessment process is designed to guard against selective reporting according to PHT degree of severity or any other potential risk factors.

CONCLUSIONS

Early and late mortality in MVS are not significantly associated with severe PHT or the addition of TVS, yet extreme PHT is associated with a higher risk of long-term mortality. Severe PHT (PASP 50-79 mm Hg) should not, in itself, cause a patient to be turned down for surgery, and concomitant TVS can be performed with no significant increase in short- or long-term mortality risks.

Conflict of Interest Statement

S. Chris Malaisrie reports nonfinancial study approval from Edwards. Sanjiv J. Shah reports consulting fees from Novartis, Bayer, AstraZeneca, and DC Devices. James D. Thomas reports personal fees from Edwards, GE, and Abbott. All other authors have nothing to disclose with regard to commercial support.

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2015/Video/Monday/04-27-15_4E_1555_Enter.mp4.

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Discussion

Dr James S. Gammie (Baltimore, Md). Thank you, Dr Girardi, Dr Puskas, and the Association for the opportunity to discuss this manuscript. Dr Enter—thank you for providing me with a copy of the manuscript well in advance. You and your colleagues have performed a retrospective study of a large series of patients undergoing mitral valve operations and have studied the impact of PHT on short- and long-term outcomes. You and your group are to be congratulated on a notably low operative mortality rate of 2.9%.

More than 70% of your patients had PHT, which you defined as a systolic pulmonary artery pressure >35 mm Hg, and you report that this group had more comorbidities, longer and more-complex operations, lower rates of mitral valve repair, and higher perioperative and long-term mortality. You went on to use propensity-score matching to compare outcomes for a matched group of 215 patients, with versus without severe PHT, which you defined as a pulmonary artery pressure of 50 to 69 mm Hg. Before you did

the propensity matching, you found that patients in the severe PHT group had an operative mortality 3 times higher than that for those without PHT. After propensity matching, however, you found that severe PHT was not independently associated with short- or long-term survival.

Dr Enter—your presentation was clear and direct and reflects your hard work and strong mentoring of an integrated resident by Dr Pat McCarthy. I have a few questions and one or two comments. Did you consider performing an analysis that excluded the mitral stenosis and the aortic valve replacement population, to more closely understand the impact of PHT on outcomes for patients with isolated mitral regurgitation? As an example, 15% of your patients had mitral stenosis, which is a pathophysiologically different disease, with a different impact of PHT on outcomes.

Dr Daniel H. Enter (*Chicago, Ill*). Thank you, Dr Gammie. It is an honor to have you review our work. As for mitral stenosis, 5% of the patients in this series had pure mitral stenosis, and 10% had mixed—mitral regurgitation and mitral stenosis. We did do an analysis excluding those 15% and found similar results: no difference in short- or long-term mortality for patients with versus without PHT.

Dr Gammie. Did you perform a multivariable regression analysis to assess the impact of PHT on short- and long-term outcomes in addition to propensity-score matching?

Dr Enter. We did not. We only performed propensity-score matching. This was chosen specifically and on the advice of our statisticians.

Dr Gammie. These data potentially have important implications for recommendations for timing of MVS, and I believe we need to be careful about drawing conclusions based on relatively small numbers, mixed etiologies, and different operations. I am not sure that your group has presented a convincing case that severe PHT is not an important risk factor for bad outcomes.

For example, in the propensity-matched group, 3% of both the no-PHT and the severe-PHT group suffered 30-day mortality. Now, 3% of 215 people is either 6 or 7 patients who died in each group, and that is a pretty small sample size on which to base strong conclusions. It may be that your analysis is underpowered to detect a mortality difference. It would be of interest to analyze pulmonary artery pressure as a continuous variable and determine what the threshold is for impact on outcomes. How do you reconcile these results that suggest no impact of PHT with other published studies showing that PHT is a powerful predictor of outcomes?

Dr Enter. This is a very good point. I think in one sense we look at this and say, well, the STS risk score doesn't already include pulmonary hypertension, why might that be? Have they looked at it and found that perhaps it's not as compared with EuroSCORE.

At our center specifically, I know there is a premium placed on myocardial protection. Surgeons have a right

ventricular temperature probe, which they monitor closely, although I am not sure why our overall rates of mortality and morbidity were lower than those in other published series.

Dr Gammie. Did you assess right-heart function and evaluate its impact on outcomes?

Dr Enter. We did not, other than pulmonary artery pressures that were presented. Those measures are usually qualitative, and not quantitative, and so we do not put very much faith in them.

Dr Gammie. Do you have any specific intra- or post-operative management strategies for patients who have PHT?

Dr Enter. The standard adjuncts of nitric oxide, milrinone, etc, can be used. But in cases in which patients are able to generate pulmonary artery pressures of 80 or 90 mm Hg, we probably use them less at our center than they are used across the country.

Dr Gammie. Finally, I would like to emphasize that your finding that pulmonary artery pressures decrease, but do not return to normal, after mitral operation reflects the fact that the presence of PHT, once established, does not completely go away, and that is important to remember, and important as we formulate our guidelines on when to intervene.

Dr Bo Yang (*Ann Arbor, Mich*). We did a similar study of mitral stenosis patients who had PHT—2 decades of experience, 317 patients. We had a similar finding for the perioperative mortality and the 30-day mortality. We did not see significant difference among the groups of normal pulmonary artery pressure: mild, moderate, and severe PHT.

However, we did find that the long-term survival in 10 or 12 years was significantly different: The group of combined moderate and severe PHT had a much lower long-term survival. The hazard ratio of death was 3-fold higher in patients who had moderate-to-severe PHT than in those with normal pulmonary artery pressure-mild PHT. We recommended that, for mitral stenosis patients who had PHT, early surgical intervention should be considered before the patients developed moderate PHT (ie, pulmonary artery pressure <45 mm Hg).

Dr Enter. Thank you. I appreciate that. If I understand you correctly, you looked at mitral stenosis. We did not look at mitral stenosis specifically, although that comprised 15% of our series.

Dr Marc Ruel (*Ottawa, Ontario, Canada*). Dr Enter—a very interesting study, but your results are contrary to so many previous publications in the valve and coronary artery bypass realms, in which it has been shown that PHT is one of the most potent predictors of perioperative mortality and long-term mortality. I think we need to understand why you came to those conclusions.

Essentially, there are 3 types of PHT, 2 of which would be captured in your study as increased systolic pulmonary artery pressures, but 1 of which might not be, and this latter type is

the patient in whom right ventricular function is so poor that it is actually not generating right ventricular systolic pressures sufficient to be classified as PHT in your study.

Within the first 2 types, ie, arterial and venous with increased measured pressures, presumably the majority of your patients had pulmonary venous hypertension, and one would expect that they would do well, and conversely, that the ones who have pulmonary arterial hypertension would not. Were you able to tease out the subclassifications of PHT so you can enlighten us?

Dr Enter. Thank you for that interesting question. The method of analysis is certainly of import here. Dr Gammie's series, and other very large ones, used multivariate analysis and had a different conclusion from ours, using propensity scoring. So that may be one relevant variable.

As to whether very high pulmonary pressures are the only ones you should use in terms of right ventricular function—this is an important point—that if your right ventricle is tired out, you might not be able to generate those 80 or 90 mm Hg pressures. So it would be interesting to look back at our data and see in the no PHT group is it bimodal in some sense and are patients who can no longer even generate those high pressures. It is not something that we have done thus far, but I would be interested in doing that evaluation.

Dr John D. Puskas (*New York, NY*). This morning, in this session, we had a vigorous discussion of tricuspid valve repair at the time of mitral repair. What were the indications for tricuspid valve repair in this study? Was it moderate or severe or mild tricuspid regurgitation or just annular dilation? Why do you think that the patients with significant PHT who had versus did not have tricuspid repair had identical 30-day and 5-year survival?

Dr Enter. Thank you for that question. The indications at our center clearly vary among the individual surgeons but follow the guidelines of moderate-to-severe tricuspid regurgitation in the setting of severe mitral regurgitation, and then PHT and annular dilation are factors in addition. I am not sure why the mortality was no different, to be honest with you.

Dr Puskas. One might have anticipated a benefit of tricuspid repair in patients who had PHT who survived their surgery. One might expect those curves to diverge at 5 years—the curves among survivors who had tricuspid repair versus those who did not have tricuspid repair—but they did not. That seems counterintuitive.

Dr Enter. Those patients were sicker patients who required the repair initially, and so that plays a role in our unmatched data. In the matched data, they have similar outcomes. I agree, we could have expected mortality differences to arise in the long-term data if tricuspid repair provided benefit.

Dr Gammie. Vinay Badhwar presented the STS data at the Conclave, and in multivariable analysis, the addition of tricuspid valve repair did not increase mortality. In fact, there was a trend toward lower mortality.

Dr Puskas. No, I would have expected a decreased mortality with repair, but we did not see that. That is what I am surprised at.

Dr Gammie. But it did not seem to adversely affect mortality, fixing the tricuspid valve. I would just mention that the vigorous discussion this morning is just another bolster and support for us to carry out a prospective randomized trial to understand in which specific situations we should be fixing the tricuspid valve.

Dr Puskas. I couldn't agree more.