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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Prevalence and Prognostic Implications of Pulmonary Hypertension in Patients With Severe Aortic Regurgitation

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ABSTRACT

BACKGROUND Pulmonary hypertension (PH) has been shown to be associated with worse outcomes in patients with aortic regurgitation (AR) in small older studies.

OBJECTIVES The authors sought to evaluate the prevalence of PH in patients with severe AR, its impact on mortality and symptoms, and regression after aortic valve replacement (AVR).

METHODS A total of 821 consecutive patients with chronic ≥ moderate-severe AR on echocardiography from 2004 to 2019 were retrospectively analyzed. PH was defined as right ventricular systolic pressure (RVSP) >40 mm Hg on transthoracic echocardiogram (mild-moderate PH: RVSP 40-59 mm Hg, severe PH: RVSP > 60 mm Hg). Clinical and echocardiographic data were extracted from the electronic medical record and echocardiographic reports. The diastolic function and filling pressures were manually assessed and checked, and the left ventricular (LV) volumes were traced by a level 3-trained echocardiographer. The primary objectives were prevalence of PH in patients with ≥ moderate-severe AR, its risk associations and impact on all-cause mortality as the primary outcome. Secondary outcomes were impact of PH on symptoms and change in RVSP at discharge post-AVR. Logistic and Cox proportional hazards regression were used to analyze these outcomes.

RESULTS The mean age was 61.2 ± 17 years, and 162 (20%) were women. Mild-moderate PH was present in 91 (11%) patients and severe PH in 27 (3%). Larger LV size, elevated LV filling pressures, and ≥ moderate tricuspid regurgitation were associated with PH. During follow-up of 7.3 (6.3-7.9) years, 188 patients died. Compared to those without PH, risk of mortality was higher in mild-moderate PH (adjusted HR: 1.59 (95% CI: 1.07-2.36) ($P = 0.021$)) and severe PH (adjusted HR: 2.90 (95% CI: 1.63-5.15) ($P < 0.001$)). Symptoms were also more prevalent in those with PH ($P = 0.004$). Of 396 patients who underwent AVR during the study period, 57 had PH. AVR similarly improved survival in patients without and with PH (P for interaction = 0.23), and there was regression in RVSP (≥8 mm Hg drop) at discharge post-AVR in 35/57 (61%) patients with PH.

CONCLUSIONS PH was present in 14% of patients with AR and was associated with higher mortality and symptoms. The survival benefit of AVR was similar in patients without and with PH. (JACC Adv 2024;3:100827)

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AVR = aortic valve replacement

LV = left ventricular

PH = pulmonary hypertension

RVSP = right ventricular systolic pressure

TR = tricuspid regurgitation

TTE = transthoracic echocardiogram

Chronic severe aortic regurgitation (AR) in later stages is associated with elevated left ventricular (LV) end-diastolic pressures which can lead to postcapillary pulmonary hypertension (PH) and over time, combined precapillary and postcapillary PH due to pulmonary vascular remodeling.[1] These patients may be denied surgery due to high surgical risk. A small old study showed a high prevalence of PH in up to 24% in patients with severe AR.[2]

Several studies have shown PH to be associated with poor outcomes in patients with other left-sided valve disease—namely, mitral stenosis and regurgitation and aortic stenosis.[3-6] In patients with severe primary mitral regurgitation, worsening PH is considered a marker of early LV decompensation and therefore mitral valve repair is indicated for rising pulmonary pressures.[7] Similarly, in aortic stenosis, severe PH has been found to be associated with increased mortality, particularly intermediate- and long-term mortality in patients undergoing surgical or transcatheter aortic valve implantation.[5,8,9] A few studies including a very small number of patients with hemodynamically significant AR or designed to evaluate other outcomes showed that PH may be associated with higher mortality in patients with AR.[10,11] In 2 smaller studies, aortic valve replacement (AVR) was associated with survival benefit despite the presence of severe PH.[2,12] There are limited data on prevalence and predictors of PH in severe AR, impact on outcomes, mortality benefit in patients with PH who undergo AVR and regression of pulmonary pressures post-AVR. We therefore sought to assess the prevalence, associated features, and impact on outcomes of PH diagnosed by Doppler echocardiography in a large, well characterized, tertiary referral contemporary cohort of patients with hemodynamically significant AR. We also evaluated whether these patients exhibit regression or reversibility of PH post-AVR.

METHODS

PATIENT POPULATION. This study was approved by the Institutional Review Board, and only patients who had provided consent to participate in research were included. We included consecutive patients with moderate-severe and severe AR who were diagnosed by comprehensive transthoracic echocardiogram (TTE) between January 2004 and April 2019. Patients with acute AR due to active endocarditis or dissection, and other etiologies of LV remodeling (moderate or more aortic or mitral stenosis, moderate or more mitral regurgitation, prior aortic or mitral valve surgery, ischemic cardiomyopathy, prior myocardial infarction, prior coronary artery bypass grafting, hypertrophic cardiomyopathy, LV assist devices, and cardiac amyloidosis) were excluded.[13] All included patients had comprehensive cardiology and/or cardiothoracic surgical evaluations within 30 days of TTE. In case of more than one TTE, the first study showing ≥ moderate-severe AR was used for analysis. The decision for AVR was based on guideline recommendations and shared decision-making by the patient, cardiologist, and cardiac surgeon.[7,14] Baseline characteristics at the time of index TTE, including demographic data, NYHA functional class, presence of symptoms (NYHA functional classes II-IV), comorbidities, Charlson comorbidity index, and recent laboratory results, were extracted from the electronic medical records.

ECHOCARDIOGRAPHY. Echocardiographic data extracted from the reports included LV size (linear dimensions and volumes) and ejection fraction, severity of AR, early diastolic mitral inflow velocity to early diastolic mitral annulus velocity, right ventricular systolic pressure (RVSP), RV size, and systolic function. The LV biplane volumes were manually traced on all the studies by a level III staff echocardiographer who was blinded to the outcomes at the time of tracing volumes. PH was defined as none (RVSP <40 mm Hg), mild-to-moderate (RVSP 41-59 mm Hg), and severe (RVSP ≥60 mm Hg).[15] RVSP was estimated by the modified Bernoulli equation using the highest (or averaged in patients with atrial fibrillation or significant respiratory variation) complete tricuspid regurgitation (TR) Doppler signal from the RV inflow, parasternal short axis, and apical views. The right atrial pressure was estimated by inferior vena cava size and respiratory collapse: 5 mm Hg when normal size and collapse, 10 mm Hg when either enlarged or reduced collapse, 15 mm Hg when both enlarged and reduced collapse, and 20 mm Hg when enlarged and no collapse. Of the original cohort of 1,100 patients,[13] TR signal was unavailable in 270 (25%) patients, so 821 patients in whom TR jet was available and RVSP could be calculated, were included in the final analyses. A detailed chart review was performed to identify an alternate etiology of PH, besides AR.

Elevated filling pressure was defined as septal E/e' >15.[16] The AR severity was determined at the time of TTE using an integrative approach, based on review of all data, including appearance and direction of the jet, effective regurgitation orifice area

TABLE 1 Baseline Characteristics

	RVSP ≤40 mm Hg	RVSP 41-59 mm Hg	RVSP ≥60 mm Hg	*P* Value
Age, y	59.9 ± 17.50	68.2 ± 14.62	70.3 ± 14.52	<0.001[a]
Female	129 (18.3%)	27 (29.7%)	6 (22.2%)	0.036[b]
BMI, kg/m^2	27.3 ± 4.53	28.4 ± 5.84	27.0 ± 5.25	0.104[a]
SBP, mm Hg	129.4 ± 18.56	138.8 ± 25.54	129.6 ± 22.47	<0.001
DBP, mm Hg	64.9 ± 12.23	61.7 ± 15.17	56.5 ± 11.90	<0.001[a]
Diabetes	67 (9.7%)	10 (11.4%)	4 (16.0%)	0.541[b]
Hypertension	323 (46.8%)	50 (56.8%)	19 (76.0%)	0.005[b]
Chronic kidney disease	42 (6.0%)	16 (17.6%)	3 (11.1%)	<0.001[b]
Chronic lung disease[d]	62 (9.0%)	13 (14.8%)	3 (12.0%)	0.209[b]
Charlson comorbidity index	1 (0-2)	1 (0-3)	2 (0-6)	0.010[c]
Symptoms at baseline	241 (34.6%)	51 (60.0%)	15 (57.7%)	<0.001[b]
NYHA functional class at baseline				<0.001[b]
I	455 (65.4%)	34 (40.0%)	11 (42.3%)	
II	167 (24.0%)	33 (38.8%)	10 (38.5%)	
III	69 (9.9%)	16 (18.8%)	4 (15.4%)	
IV	5 (0.7%)	2 (2.4%)	1 (3.8%)	
Echocardiographic variables				
LVEF	60 (56-65)	58 (50-64)	55 (45-63)	0.005[c]
LVEF <55%	145 (20.6%)	34 (37.4%)	13 (48.1%)	<0.001[b]
LVEDD	60 (56-63)	60 (55-66)	62 (52-66)	0.737[c]
LVEDD ≥65 mm	138 (19.7%)	26 (28.6%)	11 (40.7%)	0.007[b]
iLVEDD	29.8 (27.3-32.4)	31.3 (27.7-33.8)	30.2 (27.9-32.0)	0.066[c]
LVESD	39 (35-43)	42 (34-47)	40 (34-48)	0.111[c]
LVESD ≥50 mm	44 (6.4%)	14 (16.3%)	5 (20.8%)	<0.001[b]
LVESDi	19.6 (17.6-21.8)	20.6 (18.2-24.8)	20.5 (18.2-24.8)	0.015[c]
iLVESD ≥25 mm/m^2	51 (7.4%)	18 (20.9%)	6 (25.0%)	<0.001[b]
LVEDV	194 (157-240)	210 (175-285)	198 (139-264)	0.066[c]
iLVEDV	96.6 (80.5-117.5)	106.8 (86.2-136.0)	98.8 (70.9-137.3)	0.018[c]
LVESV	80 (61-104)	94 (69-133)	80 (56-167)	0.004[c]
iLVESV	39.2 (31.2-50.1)	49.7 (34.0-66.8)	45.4 (29.2-86.1)	<0.001[c]
Bicuspid aortic valve	255 (36.6%)	14 (15.4%)	3 (11.5%)	<0.001[b]
AR severity				0.711[b]
Moderate-severe	308 (43.8%)	40 (44.0%)	14 (51.9%)	
Severe	395 (56.2%)	51 (56.0%)	13 (48.1%)	
Regurgitant volume	64 (52-82)	64 (53-81)	59 (50-68)	0.390[c]
Effective regurgitant orifice area	25 (19, 33)	26 (20-32)	27 (19-40)	0.568[c]
Vena contracta	6 (5-7)	6 (5-7)	5 (5-6)	0.061[c]
≥Moderate TR	10 (1.7%)	6 (9.5%)	6 (33.3%)	<0.001[b]
E/e'	10 (8-13)	14 (10-18)	16 (12-20)	<0.001[c]
RVSP	28 (24-32)	46 (42-50)	69 (63-77)	<0.001[c]
Mid ascending aorta diameter	41 (37-45)	42 (38-45)	38 (34-50)	0.439[c]
Sinus of Valsalva diameter	40 (37-44)	41 (37-44)	39 (33-46)	0.663[c]
Elevated filling pressure	100 (15.2%)	37 (45.1%)	11 (61.1%)	<0.001[b]

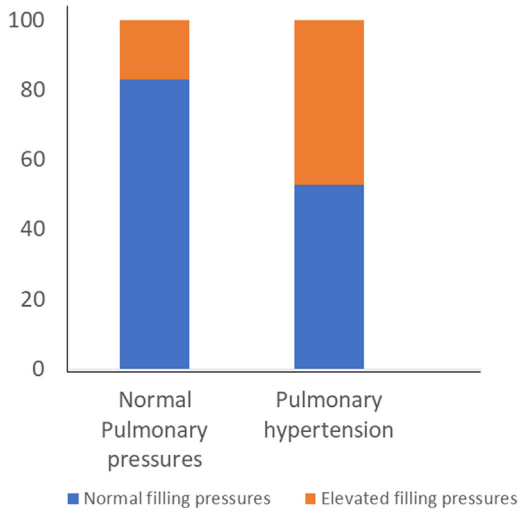
Values are mean ± SD, n (%), or median (IQR). [a]ANOVA *P* value. [b]Chi-square *P* value. [c]Kruskal-Wallis *P* value. [d]Included chronic obstructive and chronic interstitial lung diseases.

AR = aortic regurgitation; BMI = body mass index; DBP = diastolic blood pressure; E/e' = ratio of mitral inflow to mitral tissue Doppler early diastolic velocity; iLVEDD = indexed left ventricular end-diastolic dimension; iLVEDV = indexed left ventricular end-diastolic volume; iLVESD = indexed left ventricular end-systolic dimension; iLVESV = indexed left ventricular end=systolic volume; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; RVSP = right ventricular systolic pressure; SBP = systolic blood pressure; TR = tricuspid regurgitation.

and regurgitant volume assessment by proximal isovelocity surface area method or continuity equation, vena contracta, flow reversals in descending thoracic, and abdominal aorta.[17] The aorta dimensions at sinus of Valsalva and mid ascending aorta were also evaluated.

OUTCOMES. Primary outcome was all-cause mortality and primary objectives were prevalence of PH in patients with severe AR, its risk associations and impact on all-cause mortality. Secondary outcomes were impact of PH on symptoms and change in RVSP from the preoperative value to the measurement at

FIGURE 1 Left Ventricular Filling Pressures in Severe Aortic Regurgitation



Bar graphs showing prevalence of indeterminate, normal, and elevated filling pressures in patients with and without PH. Patients with PH had higher prevalence of elevated filling pressures (diastolic function grades 2-3) (59% vs 17%, $P < 0.001$) than those without PH. PH = pulmonary hypertension.

TABLE 2 Variables Associated With PH on Multivariable Analysis

	OR (95% CI)	*P* Value
Age	1.03 (1.01-1.05)	0.010
Female		0.140
iLVESV	1.03 (1.01-1.04)	<0.001
Tricuspid regurgitation (≥moderate vs <moderate)	5.08 (1.70-15.15)	0.004
Elevated filling pressures	3.40 (1.91-6.06)	<0.001

E/e' = ratio of mitral inflow to mitral tissue Doppler early diastolic velocity; iLVESV = indexed left ventricular end-systolic volume; PH = pulmonary hypertension.

the time of hospital dismissal after AVR. The vital status was retrieved using the Mayo Clinic records and Accurint, a web-based resource combining multiple national sources (queried on May 31, 2019). Patients not known to be deceased were censored at the date of the last follow-up.

STATISTICAL ANALYSIS. Data are presented as frequencies and percentages for categorical variables, and either as mean ± SD or median (IQR) for continuous variables. Groups of patients with no PH, mild-moderate PH, and severe PH were compared using chi-square test for categorical variables and analysis of variance or Kruskal-Wallis for continuous variables. The optimal cutpoint for RVSP associated with mortality was estimated using the Contal and O'Quigley method.[18] The survival curves were constructed using the Kaplan-Meier method, and groups of PH compared using the log-rank test. The curves included were adjusted for the variables in the multivariable models using a method of direct adjustment. Cox proportional hazards regression was used to examine the association of PH with mortality and AVR after adjusting for other known predictors and factors significant in the univariable analyses. These results are presented as HRs with 95% CIs. AVR was included as a time dependent covariate in the analysis of mortality. Interaction between groups of PH and AVR was examined to test for differential benefit of AVR by PH. The factors significant in univariate analyses were included in the multivariate models. Logistic regression was used to examine the association of PH with symptoms at the time of echo, and association of clinically and echocardiographically relevant variables with PH using backward selection. These results are presented with ORs and 95% CI. Changes in RVSP before or after AVR in patients undergoing AVR and over a similar time period in those not undergoing AVR were compared using paired *t*-test within group. All analyses were performed using SAS version 9.4 (SAS Institute, Inc) and *P* value <0.05 was considered statistically significant. For regression of PH, a cohort curve was plotted, and 8 mm Hg change was considered to represent a clinically meaningful difference.[19]

RESULTS

The mean age of the patients was 61.2 ± 17 years, 162 (20%) were women, 392 (49%) had hypertension, 272 (33%) had bicuspid aortic valve, and 83 (11%) had dilated ascending aorta (>5.0 cm). The cohort was divided into 3 groups, normal PA pressure (RVSP ≤40 mm Hg), mild-moderate PH (RVSP 41-59 mm Hg), and severe PH (RVSP ≥60 mm Hg). A total of 118 (14%) patients had PH: 91 (11%) had mild-moderate and 27 (3%) had severe PH. The baseline characteristics and difference between the 3 groups—normal PA pressure, mild-moderate PH, and severe PH are presented in Table 1. Patients with PH had significantly higher prevalence of elevated filling pressures compared to those with normal pulmonary pressures (59 vs 17%, $P < 0.001$) (Figure 1). The patients with PH reached more indications for surgery, that is, had larger LV size (end-systolic dimension >50 mm or indexed end-systolic dimension >25 mm/m^2 or end-diastolic dimension >65 mm) and lower ejection fraction (<55%) (Table 1).

TABLE 3 Univariable and Multivariable Predictors of Mortality in Patients With ≥ Moderate-Severe AR

		Univariable		Multivariable	
Variable	Comparison	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Right ventricular systolic pressure	41-59 vs ≤40	2.57 (1.80-3.68)	<0.001	1.59 (1.07-2.36)	0.021
	≥60 vs ≤40	5.60 (3.37-9.32)	<0.001	2.90 (1.63-5.15)	<0.001
Age		1.07 (1.06-1.08)	<0.001	1.05 (1.04-1.07)	<0.001
Female		1.66 (1.20-2.28)	0.002		0.356
Comorbidity index		1.23 (1.18-1.29)	<0.001	1.11 (1.06-1.17)	<0.001
NYHA functional class (III or IV)		2.80 (1.95-4.01)	<0.001	2.84 (1.88-4.30)	<0.001
iLVESD		1.05 (1.01-1.09)	0.015	1.04 (1.004-1.08)	0.032
AR severity (severe vs moderate-severe)		0.63 (0.48-0.84)	0.002		0.077
AVR		0.57 (0.42-0.77)	<0.001	0.64 (0.45-0.91)	0.014

AR = aortic regurgitation; AVR = aortic valve replacement; iLVESD = indexed left ventricular end-systolic dimension.

VARIABLES ASSOCIATED WITH PH. In multivariable analyses, larger LV size (indexed end-systolic volume), moderate or more TR, and elevated filling pressures were associated with presence of PH after adjusting for age and sex (Table 2). Moderate or more mitral regurgitation was excluded in this study since it can also affect the LV remodeling, and less than moderate mitral regurgitation was tested in a backward selection model and was found to be nonsignificant and removed.

On review of electronic medical record of the patients with PH, an alternate etiology of PH was present in 2 patients—one had suspected chronic thromboembolic PH who did not undergo AVR and passed away soon after diagnosis and the other had chronic obstructive pulmonary disease and paralyzed hemidiaphragm which resulted in continued elevated pulmonary pressures even after AVR. Only one patient had right heart catheterization available which showed mildly elevated pulmonary vascular resistance (3.2 WU) which was attributed to severe AR.

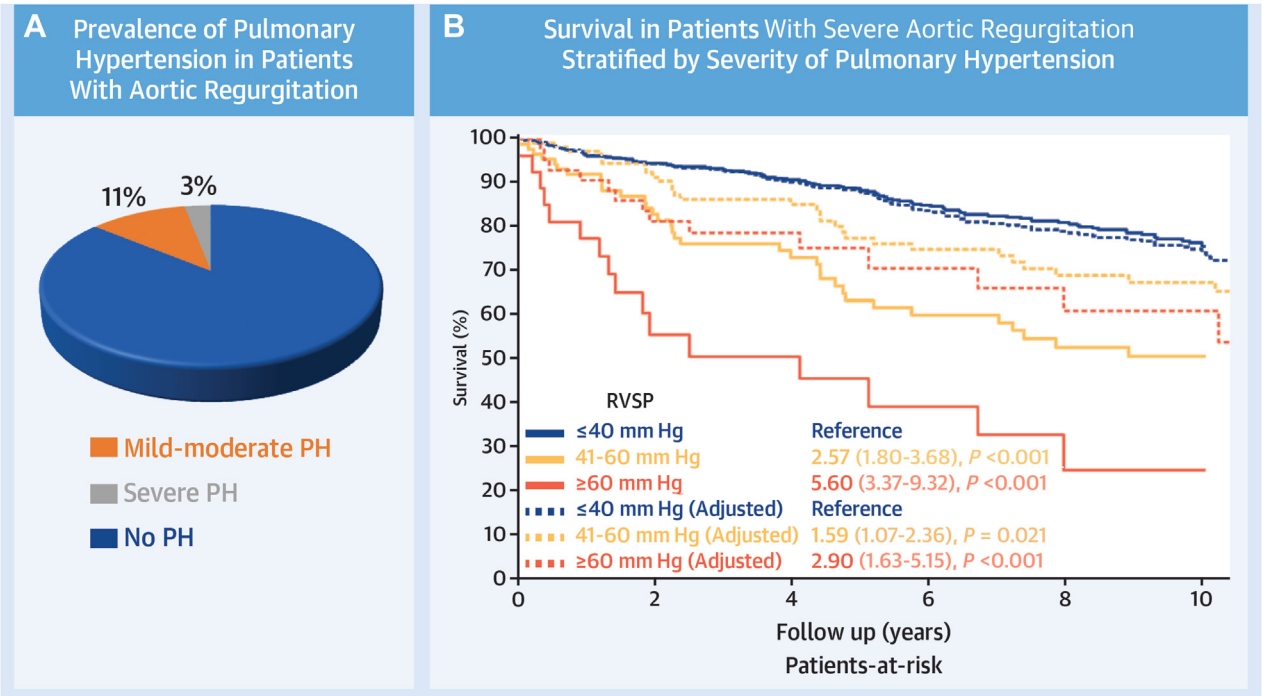
ASSOCIATION OF PH WITH MORTALITY AND SYMPTOMS. A total of 188 patients died during a median follow-up of 7.3 (IQR: 6.3-7.9) years. PH was associated with mortality in univariable and multivariable analyses (Table 3). When compared with no PH, the HR for time to death was 1.59 (95% CI: 1.07-2.36) ($P = 0.021$) for mild-moderate and 2.90 (95% CI: 1.63-5.15) ($P < 0.001$) for severe PH. Other significant factors associated with increased mortality were older age, higher comorbidity index, symptoms (NYHA functional class II-IV), and larger LV size (indexed end-systolic dimension); aortic valve surgery was associated with lower mortality (Table 3). In the Central Illustration, Kaplan-Meier survival curves show mild-moderate and severe PH were associated with increased mortality in unadjusted and adjusted models. The optimal cutpoint for excess mortality was RVSP >32 mm Hg. PH (RVSP >40 vs <40 mm Hg) was similarly associated with excess mortality in patients with NYHA functional class I or II (HR: 2.64 [95% CI: 1.81-3.84]; $P < 0.001$) and III or IV (HR: 2.69 [95% CI: 1.39-5.22]; $P = 0.003$) (P for interaction = 0.82). In addition, PH was also similarly associated with excess mortality when LV ejection fraction was preserved ≥55% (HR: 2.99 [95% CI: 2.00-4.47]; $P < 0.001$) and reduced <55% (HR: 2.54 [95% CI: 1.50-4.27]; $P < 0.001$) (P for interaction = 0.62), and in patients without any indications for surgery such as presence of symptoms, LV ejection fraction <55%, end-systolic dimension >50 mm (or >25 mm/m^2), end-diastolic dimension >65 mm (Supplemental Table 1).

PH was also associated with presence of symptoms (NYHA functional class ≥ II) (Table 4). Older age, female sex, and severity of AR (severe vs moderate-severe) were other factors associated with symptoms in multivariable model.

IMPACT OF AVR. During follow-up, 396 patients underwent AVR. These included 57 (48%) of the 118 with PH. Severe but not mild-moderate PH was associated with higher rate of aortic valve surgery. Even though PH was associated with higher mortality as described above, there was no interaction between AVR and PH groups (P for interaction = 0.23) suggesting that the AVR reduced mortality similarly in patients with normal pulmonary pressure, mild-moderate PH, and severe PH. In patients not receiving AVR, PH (RVSP >40 mm Hg) was associated with higher all-cause mortality (HR: 2.18 [95% CI: 1.40-3.38]; $P < 0.001$) when compared to no PH or RVSP <40 mm Hg.

CHANGES IN PULMONARY PRESSURES OVER TIME. Dismissal echocardiogram (echocardiogram performed just prior to hospital discharge post-AVR) was performed in 309/396 patients. Fifty-four (13.6%) of

CENTRAL ILLUSTRATION **Pulmonary Hypertension in Patients With Severe Aortic Regurgitation**



Anand V, et al. JACC Adv. 2024;3(3):100827.

(A) Pulmonary hypertension (PH) was prevalent in 14% patients with ≥moderate-severe AR with mild-moderate PH (right ventricular systolic pressure [RVSP] 41-60 mm Hg) in 11% and severe PH (RVSP >60 mm Hg) in 3%. (B) PH was associated with all-cause mortality in both unadjusted (solid lines) and adjusted (dashed lines) Kaplan-Meier analysis. Patients with higher RVSP had higher all-cause mortality in unadjusted model and after adjusting for age, sex, comorbidity index, NYHA functional class, indexed left ventricular-end systolic dimension, aortic regurgitation severity and aortic valve replacement. HRs were 1.59 (95% CI: 1.07-2.36; $P = 0.021$) and 2.90 (95% CI: 1.63-5.15; $P < 0.0001$), for mild-moderate and severe PH, respectively. AR = aortic regurgitation.

these 396 patients who underwent AVR had decrease in RVSP (≥8 mm Hg).

Of the 57 patients with PH who underwent AVR, 35 (61%) had a significant decrease in their pulmonary pressures on dismissal echo (≥8 mm Hg), and 26 of these 35 (74%) patients who had a significant decrease in RVSP had pulmonary pressures that returned to normal on dismissal echo (<40 mm Hg). Four additional patients who had stable pressures (within 8 mm Hg drop) had dismissal RVSP <40 mm Hg. Out of the remaining 22 patients, RVSP was stable in 11 patients (within 8 mm Hg change), unavailable in 10 patients (due to lack of TR jet or TTE), and increased significantly in 1 patient who had severe chronic obstructive pulmonary disease and paralyzed hemidiaphragm which resulted in group 3 PH in addition to group 2 due to severe AR.

In the cohort of patients with PH who did not undergo AVR (61/118, 52%), mean change in RVSP within 12 months was nonsignificant (n = 14, −1 ± 14 mm Hg, $P = 0.87$). The pulmonary pressures remained stable over time in 7 patients, decreased ≥8 mm Hg in 4 patients, and increased ≥8 mm Hg in 3 patients. Using Kaplan-Meier analysis, of the patients who did not have PH at baseline and had at least 1 follow-up echo (n = 567), an estimated 21% (IQR: 17%-26%) of patients developed PH at 5 years.

There was higher prevalence of elevated filling pressures preoperatively in patients who had significant drop in RVSP postoperatively (Table 5). After adjusting for age, sex, ejection fraction, indexed end-systolic volume and dimension, elevated LV filling pressures was the only significant factor in multivariable analysis significantly associated with regression in PH.

DISCUSSION

In this large tertiary referral contemporary cohort of moderate-severe and severe AR patients, Doppler

echocardiography derived PH as defined by RVSP >40 mm Hg was present in 14% patients, and severe PH (RVSP ≥60 mm Hg) in 3%. The optimal cutoff of 32 mmHg derived from our analysis was similar to the threshold of 30 mm Hg previously shown to be associated with increased mortality in a large, unselected cohort of patients undergoing clinically indicated echocardiography.[15] The factors associated with PH in these patients were larger LV size, ≥ moderate TR, and elevated filling pressures. PH was associated with mortality, symptoms, and AVR. The patients with and without PH benefitted from AVR, with a reduction in mortality with AVR. Of those with PH at diagnosis, pulmonary pressures regressed post-AVR at dismissal in 61% patients.

PREVALENCE AND RISK ASSOCIATIONS. PH is common in left-sided valvular disease and has been studied extensively in patients with mitral stenosis and regurgitation and aortic stenosis, but the data in AR are limited.[3,20,21] PH (RVSP >50 mm Hg) is considered Class IIa recommendation for mitral valve repair in patients with primary severe mitral regurgitation suggesting the elevated pulmonary pressures are a sign of early decompensation.[7,14,22] In the current study, we evaluated the prevalence and impact of PH in patients with severe AR in a large contemporary cohort; the prevalence of mild-moderate PH and severe PH was 11% and 3%, respectively. The prevalence is lower than in a smaller prior study which reported 16% prevalence of severe PH in their cohort using similar echocardiographic RVSP cutoff.[12] Another older study also reported a somewhat higher prevalence of 24% of severe PH (RVSP >60 mm Hg) using right heart catheterization.[2] The patients in these 2 studies[2,12] had larger LV size, lower ejection fraction, and higher LV end-diastolic pressures for a longer period and likely were evaluated later in the course of disease. The factors associated with PH in our study, larger LV size, elevated filling pressures, and ≥moderate TR, are similar to those observed in a smaller study from 1991.[2] These factors suggest higher filling pressures perhaps due to decompensation, and onset of myocardial damage which happens later in the disease course. This is also studied in patients with mitral regurgitation, where left atrial and pulmonary pressures are not substantially elevated in the chronic compensated stage and begin to rise with the onset of decompensation—decline in left atrial compliance or occult systolic/diastolic dysfunction.[6] The prevalence of PH noted in our cohort of severe AR is slightly lower than what is observed in primary mitral regurgitation (14% vs 23%).[23] Mitral regurgitation was not associated with PH in this study as patients with ≥ moderate mitral regurgitation were excluded, since it can also affect LV remodeling.

The association of higher filling pressures with PH suggests postcapillary PH, although systematic right heart catheterization was not performed/available due to retrospective analyses. There are many causes of PH-idiopathic or a result of drug, toxin, or infection exposure, congenital heart disease, secondary to heart disease, lung disease or hypoxia, chronic thromboemboli, connective tissue disorder, and miscellaneous causes.[24] Although the current study did not investigate and systematically rule out these causes, most patients in this cohort likely had PH due to cardiac causes, since alternate causes of PH were identified in only 2 patients by thorough chart review. Since the current guidelines recommend AVR for symptoms or drop in ejection fraction (<55%) or significant LV remodeling (end-diastolic dimension >65 mm and end-systolic dimension >50 mm) which occurs later in the disease course, the higher prevalence of PH and risk associations including larger LV

TABLE 4 Association of Right Ventricular Systolic Pressure With Symptoms

	Comparison	OR (95% CI)	*P* Value
Right ventricular systolic pressure	41-59 vs ≤40	2.08 (1.27-3.40)	0.004
	≥60 vs ≤40		0.260
Age		1.02 (1.01-1.03)	<0.001
Female		1.96 (1.35-2.82)	<0.001
Comorbidity index			0.884
iLVESD		1.04 (0.99-1.08)	0.096
AR severity (severe vs moderate-severe)		1.38 (1.01-1.89)	0.044

AR = aortic regurgitation; iLVESD = indexed left ventricular end-systolic dimension.

TABLE 5 Factors Associated With Change in Right Ventricular Systolic Pressure on Dismissal When Compared to Pre-AVR

	≥8 mm Hg Decrease	Between −8 and 8 mm Hg	≥8 mm Hg Increase	*P* Value
Age	58.8 ± 16.38	58.6 ± 16.4	57.3 ± 15.86	0.853[a]
Female	13 (24.1%)	34 (17.8%)	9 (14.1%)	0.365[b]
LVEF	57 (51-64)	60 (54-65)	60 (56-63)	0.280[c]
Elevated filling pressures	14 (30.4%)	30 (17.0%)	5 (8.5%)	0.013[b]
iLVESD	19.8 (17.8-25.0)	20.3 (18.1-22.8)	20.6 (17.8-22.4)	0.903[c]
iLVESV	48.7 (35.5-55.8)	42.5 (33.3-56.5)	41.7 (33.9-54.3)	0.331[c]

Values are mean ± SD, n (%), or median (IQR). [a]ANOVA *P* value. [b]Chi-square *P* value. [c]Kruskal-Wallis *P* value.
E/e' = ratio of mitral inflow to mitral tissue Doppler early diastolic velocity; iLVESD = indexed left ventricular end-systolic dimension; iLVESV = indexed left ventricular end-systolic volume.

size and higher filling pressures, are not surprising, and supported by our analyses showing patients with PH had higher prevalence of indications for surgery.

PH AND OUTCOMES. Studies in other left-sided valvular diseases have shown that elevated pulmonary pressures are associated with poor outcomes.[3,5,6,23] The data on the impact of PH on outcomes in a contemporary cohort of patients with AR are lacking. Our study showed that PH is associated with mortality in both unadjusted model and after adjusting for other known risk factors, and in patients without any indications for AVR. The association was stronger with severe PH than mild-moderate PH. PH was also associated with the presence of symptoms and higher NYHA functional class, and patients with PH more often had AVR. These findings highlight the importance of a careful assessment of pulmonary pressures in patients with hemodynamically significant AR during echocardiography, and the potential role of PH in risk stratification and determining the timing for surgery after validation in prospective studies.

THE EFFECT OF AVR. Based on visual inspection of the survival curves, both early and late mortality was higher in patients with PH than those without. However, the benefit of AVR was noted in all groups—without PH, mild-moderate PH, and severe PH, with lower mortality in patients who underwent AVR. The patient numbers were very small to perform adjusted analysis. These results highlight that benefit of AVR on mortality is similar in patients with and without PH, and surgery should not be deferred in patients with PH solely for their elevated pulmonary pressures. Our results suggest that patients with elevated pulmonary pressures may even benefit from early intervention if they have not met other criteria for intervention; however, this needs to be studied in larger prospective studies.

STUDY LIMITATIONS. Our study has several limitations—retrospective study design limits assessment of predictors and only risk associations can be determined (vs causality), there is possible referral bias, and lack of follow-up data on 13% patients beyond 1 year because of large referral center. The TR jet was unavailable in around 25% of the patients from the original cohort and it may change the true prevalence of PH in this population. Hemodynamic right heart catheterization was not available for these patients so the number of patients with post and combined post- and pre-post capillary PH could not be assessed. Furthermore, no adjustments were made to CIs or *P* values to account for multiple comparisons so results should be interpreted with caution.

CONCLUSIONS

In patients with > moderate AR, PH was present in 14% and was severe (RVSP 60 mm Hg) in 3%. The factors associated with PH included larger LV size, elevated LV filling pressures, and ≥ moderate TR. When present, PH was associated with higher all-cause mortality and symptoms. Even though the mortality was higher in patients with PH than those without, the benefit of AVR was present in all 3 patient groups—no PH, mild-moderate PH, and severe PH. The pulmonary pressures decreased significantly (≥8 mm Hg) in nearly two-thirds of patients post AVR at dismissal. There is a need for larger prospective studies to study the trends in RVSP post-AVR and if elevated PA pressures may be considered as a criterion for early intervention in patients with severe AR.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with severe AR, PH was present in 14% and was associated with higher all-cause mortality and symptoms. The survival benefit of AVR was similar in patients without and with PH, and pulmonary pressures regressed significantly in 61% patients post-AVR.

TRANSLATIONAL OUTLOOK: Larger prospective studies are needed to study if elevated pulmonary pressures may be considered as a criterion for early intervention in low surgical risk patients with severe AR.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.