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# Pulmonary hypertension is a manifestation of congestive heart failure and left ventricular diastolic dysfunction in octogenarians with severe aortic stenosis

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**Abstract:** Previous studies have suggested that pulmonary hypertension (PH) in severe aortic stenosis (AS) is a risk factor for operative mortality with aortic valve replacement (AVR). Conversely, others have shown that patients with AS and PH extract a large symptomatic and survival benefit from AVR compared with those patients not treated surgically. We sought to evaluate the prevalence, severity, and mechanism of PH in an elderly patient cohort with severe AS. We prospectively evaluated 41 patients aged  $\geq 80$  years with severe AS. All patients underwent cardiac catheterization and transthoracic echocardiography within 24 hours. We found that PH was common in this cohort: 32 patients (78%) had PH; however, the predominant mechanism of PH was left heart congestion. Patients with PH had nearly double the pulmonary artery wedge pressure of patients without PH (23 vs. 13 mmHg;  $P \leq 0.001$ ). In patients with PH compared with those without, pulmonary vascular resistance was higher yet still under 3 Wood units (WU; 2.9 vs. 1.5 WU;  $P = 0.001$ ), and the transpulmonary gradient (11 vs. 7 mmHg;  $P = 0.01$ ) and diastolic pulmonary gradient (DPG; 3.0 vs. 2.7 mmHg;  $P = 0.74$ ) were in normal range. Left ventricular diastolic abnormalities were more common in patients with severe AS and PH. Right ventricular (RV) dysfunction was common (13/41 patients, 32%), but the PH and non-PH groups had similar tricuspid annular plane systolic excursion (2.0 vs. 2.3 cm;  $P = 0.15$ ). Only 2 subjects had both RV dysfunction and an elevated DPG. In conclusion, PH is common in elderly patients with severe AS. This occurs largely due to left heart congestion, with a relative absence of pulmonary vascular disease and RV dysfunction, and as such, PH may serve as a heart failure equivalent in these patients.

**Keywords:** aortic stenosis, pulmonary hypertension, congestive heart failure, diastolic dysfunction.

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Severe aortic stenosis (AS) is encountered with increasing frequency in industrialized nations. This is in part due to aging population demographics but also may be due to increased awareness of the diagnosis in light of emergence of transcatheter aortic valve replacement (TAVR).<sup>1-3</sup>

In patients with severe AS, significant pulmonary hypertension (PH) has often been considered a relative contraindication to AVR as a result of increased operative mortality.<sup>4-7</sup> However, other studies have shown that patients with severe AS and PH extract a significant symptomatic and survival benefit with AVR compared to those patients treated medically.<sup>8,9</sup>

Importantly, PH is common in adult patients with severe AS, with prevalence ranging between 25% and 65%.<sup>4,10-12</sup> However, it should be noted that most studies evaluating the prognosis of patients with PH and severe AS have used Doppler-estimated pulmonary artery systolic pressures (PASPs) obtained via tricuspid regurgitant (TR) jet velocity from transthoracic echocardiography (TTE), which may both under- and overestimate the presence

of PH.<sup>13</sup> In addition to accuracy limitations, Doppler-estimated PASP alone does not provide insight into the hemodynamic mechanism of PH in any given patient or the presence or absence of an elevated pulmonary vascular resistance (PVR) and right ventricular (RV) dysfunction, all of which likely better inform regarding a patient's PH-related risk with valvular intervention.

The few studies to use invasive hemodynamic assessment to characterize PH in patients with severe AS typically evaluated younger patients (before the TAVR era), and the physiology of PH in elderly patients being evaluated for TAVR might be quite different from that in younger cohorts, as elderly patients often have a variety of risk factors for PH aside from AS, such as systemic hypertension, renal dysfunction, sleep apnea, and left ventricular (LV) diastolic dysfunction. Importantly, prior invasive hemodynamic studies did not simultaneously evaluate LV structure, systolic and diastolic parameters, or RV function in patients with and without PH.<sup>10-12</sup>

This study was therefore designed with the following aims: (1) to evaluate the prevalence of PH based on both invasive he-

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modynamic assessment and TTE in an elderly cohort with severe AS, (2) to determine the predominant mechanism of PH in these patients and find associations between invasive hemodynamics and LV systolic and diastolic abnormalities on TTE, and (3) to evaluate for the presence of RV dysfunction and elevated PVR in patients with and without PH.

## METHODS

All patients aged 80 years and older referred for cardiac catheterization at the University of Pennsylvania over a 6-month period to assess AS of at least moderate severity in consideration of TAVR evaluation were screened for enrollment in this study. Patients were excluded if they had a bicuspid aortic valve, moderate or greater aortic regurgitation, severe mitral regurgitation or stenosis, severe oxygen-dependent chronic obstructive pulmonary disease, or prior aortic or mitral valve surgery or were hemodynamically unstable. The protocol was approved by the University of Pennsylvania Institutional Review Board (IRB approval 811936), and all patients provided written informed consent.

## Echocardiography

Standard 2-dimensional (2D) and Doppler TTEs were obtained using Philips IE33 machines (Philips Medical Systems) within 24 hours of invasive hemodynamic assessment. LV dimensions, LV wall thickness, and left atrial anterior-posterior dimensions were measured from the parasternal long-axis view in 2D in standard fashion. Left ventricular outflow tract (LVOT) dimension was measured in 2D in the parasternal long-axis view in midsystole. Peak and mean aortic valve gradients were measured using continuous-wave Doppler (including use of a Pedoff nonimaging continuous-wave probe) from standard echocardiographic views. In addition, LVOT and aortic valve velocity time integrals (VTIs) were measured in all patients. For those in atrial fibrillation, an average of 5 cycles was used.

LV ejection fraction (LVEF) was calculated using the biplane Simpson method of disks. Pulse wave (PW) Doppler of mitral valve inflow was used as a measure of LV diastolic function. RV systolic function was measured using tricuspid annular plane systolic excursion (TAPSE) via the M-mode of the tricuspid annulus. In addition, PASP was estimated using TR jet velocity added to an estimate of right atrial pressure per American Society of Echocardiography guidelines.<sup>14</sup> PH based on TTE assessment was defined as estimated PASP >40 mmHg. Last, the VTI of the PW spectral Doppler signal in the RV outflow tract (RVOT) was measured from parasternal short-axis views in all patients, and the presence of Doppler notching of this PW signal was also assessed in all patients.<sup>15</sup>

## Cardiac catheterization

All patients underwent right and left heart catheterization via a standard femoral approach using 6-French catheters. Aortic valve gradients were measured using a fluid-filled, dual-lumen pigtail catheter with simultaneous measurement from the left ventricle and proximal ascending aorta. For patients in atrial fibrillation, an average of 5 cycles was used with AV gradients and hemodynamic measurements. All hemodynamic measurements were collected within 3 minutes of

valve gradient assessment at end expiration. PH was defined as mean PA pressures >25 mmHg. Oxygen consumption ( $\dot{V}O_2$ ) was directly measured using an Ultima Cardio<sub>2</sub> breathing analyzer (Medgraphics).

## Statistical analysis

Patients were classified as having PH–right heart catheterization (PH-RHC) or no PH–right heart catheterization (NoPH-RHC) on the basis of invasive hemodynamics. Demographic, clinical, hemodynamic, and echocardiographic variables were compared between the PH-RHC group and the NoPH-RHC group. In addition, in the PH-RHC group, we evaluated the performance of Doppler-estimated PASP in correctly identifying patients with PH. Continuous variables were compared with a *t* test, using a paired-samples technique where appropriate. Discrete variables were compared using the Fisher exact test. All significance tests were 2-sided, and *P* < 0.05 was considered significant.

## RESULTS

Forty-one patients (mean age: 86 ± 5 years) with severe AS (aortic valve area: 0.72 cm<sup>2</sup>) were enrolled in the study. Clinical and demographic characteristics of the overall cohort and those with and without PH characterized by invasive hemodynamic assessment are shown in Table 1. PH was common in this cohort: 32 patients (78%) met criteria for PH on hemodynamic assessment.

Table 1. Clinical and demographic characteristics of the study cohort

	Overall ( <i>n</i> = 41)	PH-RHC ( <i>n</i> = 32)	NoPH-RHC ( <i>n</i> = 9)	<i>P</i>
Age, mean ± SD, years	86 ± 5	86 ± 5	86 ± 4	0.70
Male, %	49	47	56	0.72
Weight, mean ± SD, pounds	166 ± 39	165 ± 39	168 ± 41	0.85
BSA, mean ± SD, m <sup>2</sup>	1.8 ± 0.3	1.8 ± 0.2	1.8 ± 0.3	0.84
HTN, %	73	75	67	0.68
Heart failure, %	88	91	78	0.29
Syncope, %	20	16	33	0.34
Angina, %	22	22	22	0.65
CAD, %	63	66	56	0.70
DM, %	10	19	22	0.99
PAD, %	17	22	0	0.31
Afib, %	39	44	22	0.44

Note: Afib: atrial fibrillation; BSA: body surface area; CAD: coronary artery disease; DM: diabetes mellitus; HTN: hypertension; NoPH-RHC: no pulmonary hypertension–right heart catheterization; PAD: peripheral arterial disease; PH-RHC: pulmonary hypertension–right heart catheterization; SD: standard deviation.

Table 2. Invasive hemodynamic characteristics of the study cohort

	Overall cohort (n = 41)	PH-RHC (n = 32)	NoPH-RHC (n = 9)	P
RAP, mmHg	9 ± 4	10 ± 4	7 ± 3	0.01
PA systolic pressure, mmHg	47 ± 15	52 ± 12	29 ± 5	<0.001
PA diastolic pressure, mmHg	23 ± 7	25 ± 6	16 ± 3	<0.001
Mean PA, mmHg	31 ± 9	34 ± 8	20 ± 3	<0.001
PAWP, mmHg	21 ± 7	23 ± 6	13 ± 4	<0.001
TPG, mmHg	10 ± 5	11 ± 5	7 ± 4	0.01
DPG, mmHg	2.9 ± 3.3	3.0 ± 3.4	2.7 ± 2.8	0.74
RAP/PAWP ratio	0.45 ± 0.15	0.44 ± 0.15	0.50 ± 0.13	0.32
Cardiac output, L/min	4.2 ± 1.2	4.1 ± 1.2	4.5 ± 1.2	0.47
PVR, WU	2.6 ± 1.5	2.9 ± 1.5	1.5 ± 0.8	0.001
SVR, WU	23 ± 7	24 ± 8	21 ± 7	0.34
PVR/SVR ratio	0.11 ± 0.07	0.12 ± 0.07	0.07 ± 0.05	0.05
Aortic valve area, cm <sup>2</sup>	0.71 ± 0.31	0.69 ± 0.29	0.77 ± 0.37	0.53
Aortic peak gradient, mmHg	37 ± 22	36 ± 23	41 ± 20	0.48
Aortic mean gradient, mmHg	44 ± 17	44 ± 17	46 ± 15	0.72

Note: DPG: diastolic pulmonary gradient; NoPH-RHC: no pulmonary hypertension–right heart catheterization; PA: pulmonary artery; PAWP: pulmonary artery wedge pressure; PH-RHC: pulmonary hypertension–right heart catheterization; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SVR: systemic vascular resistance; TPG: transpulmonary gradient; WU: Wood units.

Patients in the PH-RHC group were similar to those in the NoPH-RHC group in terms of age, sex, weight, and body surface area. Though patients with PH more commonly had systemic hypertension, symptoms of heart failure, prior history of coronary artery disease, and history of atrial fibrillation, these differences were not statistically significant compared with NoPH-RHC patients in this cohort (Table 1).

Hemodynamic characteristics of the study groups are shown in Table 2. Most PH-RHC patients (72%) had mild or moderate PH (defined as PASP 40–59 mmHg), while 28% had severe PH (defined as PASP ≥60 mmHg).

The predominant mechanism of PH in this cohort was left heart congestion. Patients in the PH-RHC group had nearly double the pul-

monary artery wedge pressure (PAWP) of patients in the NoPH-RHC group, with a higher PVR that was still under 3 Wood units (WU). The transpulmonary gradient (TPG) and diastolic pulmonary gradient (DPG) were both in the normal range in the PH-RHC and NoPH-RHC groups. The ratio of RA pressure to PAWP was also similar between the PH-RHC group and the NoPH-RHC group, as was PVR/systemic vascular resistance ratio (Table 2). Of the 14 patients in the PH group with PVR >3 WU, 10 patients (71%) had normal DPG ≤7 mmHg. Mean DPG in the PVR >3 WU group was 5.4 mmHg.

Echocardiographic characteristics of the study cohort are illustrated in Table 3. PASP estimated by TTE was significantly higher in the PH-RHC group than in the NoPH-RHC group. However, TTE underestimated the degree of PH relative to RHC in the PH-RHC patients. Moreover, if we used only TTE, 10 patients (31%) in the PH-RHC group would have been misclassified as not having PH if using TTE alone, though none of these patients had severe PH. Patients in the PH-RHC group had more LV hypertrophy, higher mitral E wave velocities, and higher E/A ratios, in keeping with LV diastolic dysfunction and elevated LV filling pressure. LV diastolic dimension and LVEF were not significantly different in patients with PH compared with patients without PH (see Table 3).

In the overall cohort, 13 patients (32%) had evidence of RV dysfunction (defined as TAPSE <1.8 cm), yet the average TAPSE value was not significantly different between the PH-RHC group and the NoPH-RHC group. Figure 1 illustrates the interactions of TAPSE and PVR and of TAPSE and DPG in patients with PH. Most patients

Table 3. Echocardiographic characteristics of the study cohort

	Overall cohort (n = 41)	PH-RHC (n = 32)	NoPH-RHC (n = 9)	P
LVEF, %	58 ± 17	56 ± 18	64 ± 11	0.12
LV EDD, cm	4.42 ± 0.98	4.38 ± 1.0	4.59 ± 0.68	0.47
LV PW Doppler, cm	1.36 ± 0.67	1.43 ± 0.74	1.12 ± 0.21	0.046
LA size, mm	43 ± 8	44 ± 8	39 ± 8	0.15
E wave velocity, m/s	1.06 ± 0.41	1.13 ± 0.4	0.79 ± 0.15	0.001
E/A ratio	1.07 ± 0.57	1.21 ± 0.6	0.7 ± 0.1	0.001
TAPSE, cm	2.0 ± 0.5	2.0 ± 0.5	2.3 ± 0.5	0.15
RVOT VTI, cm	15 ± 3.5	14 ± 3	18 ± 3	0.02
RVOT Doppler notching, %	25	31	0	0.29
Acceleration time, ms	101 ± 22	100 ± 24	104 ± 14	0.57

Note: EDD: end diastolic dimension; LA: left atrium; LV: left ventricular; LVEF: left ventricular ejection fraction; NoPH-RHC: no pulmonary hypertension–right heart catheterization; PH-RHC: pulmonary hypertension–right heart catheterization; PW: pulse wave; RVOT: right ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion; VTI: velocity time integral.

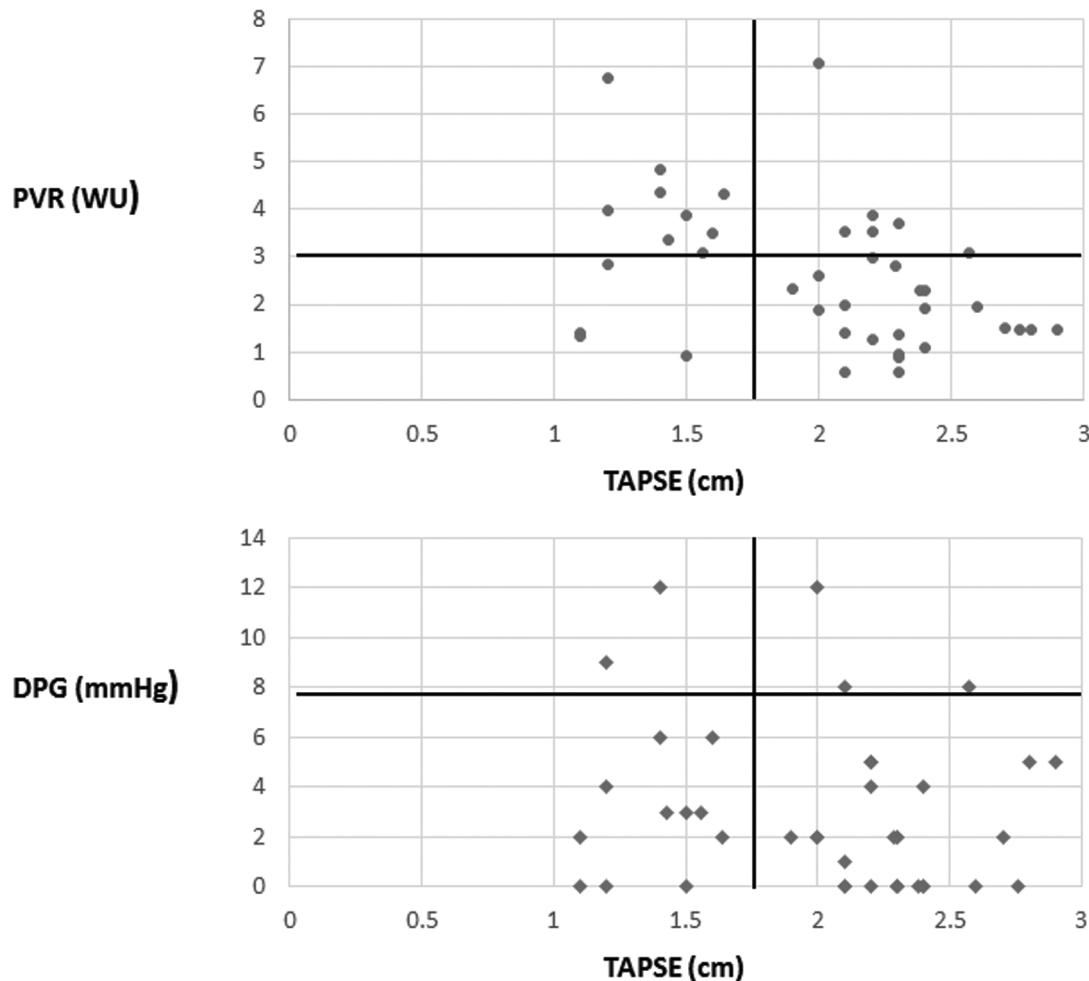


Figure 1. Scatterplot of tricuspid annular plane systolic excursion (TAPSE) versus pulmonary vascular resistance (PVR; *top*) and diastolic pulmonary gradient (DPG; *bottom*). WU: Wood units.

with PH fell into the normal-TAPSE, low-PVR quadrant, whereas only 9 patients (28%) had both elevated PVR and RV dysfunction. More importantly, however, only 2 patients had RV dysfunction and an elevated DPG.

The RVOT VTI was lower in patients in the PH-RHC group than in the NoPH-RHC group (see Table 3). Notching of the PW Doppler profile in the RVOT was uncommon in the PH-RHC group and completely absent in the NoPH-RHC group, and RVOT acceleration time was similar in both groups, in keeping with overall normal PVR. Midsystolic notching and RVOT acceleration time <80 ms correctly identified both patients with PVR >5 WU.

## DISCUSSION

In this study, we demonstrated that PH was present in the vast majority of elderly patients with severe AS and is typically a reflection of worsened left heart congestion and LV diastolic dysfunction, with a relative absence of pulmonary vascular remodeling. Severe calcific AS is most commonly encountered in elderly patients, and even the very elderly are increasingly being evaluated for valvular intervention and given less invasive and even percutaneous aortic valve

replacement.<sup>16,17</sup> Likewise, PH is prevalent in the setting of severe AS, with prior literature showing that PH is associated with increased perioperative risk and also that patients with PH and severe AS extract a large symptomatic and survival benefit from AVR.<sup>4-9</sup>

The former observation could suggest that PH itself is the cause of increased risk in the setting of AVR. However, such observations may also reflect the fact that elderly patients with AS often have a variety of comorbid conditions that are also associated with PH (i.e., systemic hypertension, arteriosclerosis, coronary artery disease, chronic kidney disease, sleep apnea), and it is these factors and not PH per se that convey risk in this setting.<sup>18,19</sup>

The latter observation is likely explained by the high prevalence of left-sided heart failure (HF) in severe AS, a powerful adverse prognostic factor in AS offset by corrective valve surgery.<sup>20</sup> Therefore, it is critically important to distinguish the mechanism of PH in the setting of severe AS.

Our study is the first, to our knowledge, to rigorously evaluate the prevalence and mechanisms of PH in an elderly cohort with severe AS by using concomitant invasive hemodynamic assessment and echocardiographic-Doppler assessment. Our findings confirm that

PH is very commonly encountered in elderly patients with AS, with a prevalence at 78%, which is even higher than reported in previously studied younger cohorts.<sup>4,10-12</sup>

In terms of the mechanism of PH in these patients, previous hemodynamic studies have reported varied findings. Silver et al.<sup>12</sup> evaluated 45 patients with severe AS and found only 13 patients (29%) to have PH, based on PASP >50 mmHg. In this study, patients with PH had lower LVEF and cardiac index. Interestingly, most of these patients also had elevated TPG, implying a reactive component of component of pulmonary vascular remodeling.

Faggiano et al.<sup>10</sup> studied a larger cohort of 388 younger AS patients (mean age: 67 years) characterized by hemodynamic evaluation. In their study, PH was more prevalent, with 75% of patients having some degree of PH. PA pressures correlated most strongly with left ventricular end diastolic pressure and PAWP. There was no significant correlation between PH and LVEF in their study. TPG was again higher in patients with PH, especially those with severe PH.

In our elderly cohort, elevated left heart pressures were the predominant driver of PH. Interestingly, RA pressure to PAWP ratio was relatively low and in fact lower in the patients with PH than in those without PH, again suggesting a high burden of left heart congestion and a relative absence of disproportionate right heart failure in these patients. TPG was higher in patients with PH but still overall in the normal range, while DPG was similar and normal in both groups, and even those patients with PVR >3 WU typically had normal DPG.

In addition, our study also demonstrated significant differences in LV structure, with more left ventricular hypertrophy and a greater degree of diastolic dysfunction in patients with PH, confirming the hemodynamic findings. In keeping with a lack of difference in cardiac index between patients with and without PH, we did not find a significant association between PH and LV systolic function. Moreover, while RV dysfunction was relatively common in this cohort (32%), TAPSE values were similar in the PH and non-PH groups.

Moreover, even among patients with PH, the prevalence of patients with RV dysfunction and elevated PVR was relatively low, while the presence of RV dysfunction and an elevated DPG was rare. Thus, the combined presence of RV dysfunction and true pulmonary vascular disease, which should embody a higher-risk PH population, was distinctly uncommon. Finally, though TTE underestimated the prevalence of PH, echocardiographic-Doppler estimates of PVR were able to correctly identify patients with severely elevated PVR.

### Limitations

Our study has several important limitations. Because of the careful and rigorous requirement for TTE and invasive hemodynamic assessment within 24 hours, our sample size was relatively small, and this may have been responsible for a lack of statistical significance in some variables, particularly in terms of clinical and demographic variables. Though we collected clinical data on typical risk factors for PH, not all patients had a detailed evaluation for other etiologies of PH such as chronic thromboembolic PH or PH related to

chronic lung disease such as chronic obstructive pulmonary disease, although no patients were oxygen dependent in this study. In addition, though patients with severe mitral stenosis or regurgitation or prior mitral surgery were excluded, we did not quantitatively assess mitral regurgitation in our cohort.

### Conclusions

In summary, the predominance of left-sided congestion and absence of pulmonary vascular disease by hemodynamics, the greater burden of left-sided structural heart disease and diastolic dysfunction by echocardiographic-Doppler exam, and the relatively low incidence of concomitant RV dysfunction and elevated PVR speak to the fact that in most elderly subjects with PH, the PH represents a left-sided HF equivalent in the setting of severe AS in these patients. This concept has several implications with regard to the assessment and management of elderly patients with severe AS and PH. First, in those elderly patients with severe AS and PH not felt to be surgical or TAVR candidates, cautious management of preload and afterload might decrease left heart congestion, reduce PA pressures, and hopefully lead to symptomatic improvement. A similar strategy might be employed to medically optimize elderly patients with AS and PH prior to surgical AVR or TAVR therapy, weighing the risks of medical management with the delay to their definitive intervention. Last, we hypothesize that elderly patients with severe AS and PH would obtain a significant symptomatic benefit from AVR and that over time their PA pressures would decrease.

A recent published report from the FRANCE 2 TAVR registry serves to support this notion. In the French registry, patients with PH had no difference in 30-day mortality or major adverse cardiovascular events after TAVR. Patients with PH did have higher 1-year mortality than patients without PH, but functional status and symptoms improved after TAVR regardless of PA pressure.<sup>8</sup> Similarly, Sinning et al.<sup>21</sup> reported that a reduction in PA pressure after TAVR was associated with improvement in 2-year mortality. Ultimately, we hypothesize that PH, as a left-sided HF equivalent, may represent more of an indication rather than a contraindication for valvular intervention, including TAVR, in most elderly patients with severe AS, though larger prospective studies are clearly warranted to assess outcomes postvalvular intervention in this population.

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**Conflict of Interest:** None declared.

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