

## Right ventricle to pulmonary artery coupling in moderate aortic stenosis: association with outcome

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**Funding Acknowledgements:** None.

**Background:** Right ventricular–pulmonary artery (RV-PA) coupling, which reflects matching of RV contractility over pulmonary resistance and measured by echocardiography as the ratio of tricuspid annular plane systolic excursion (TAPSE) and systolic PA pressure (sPAP), has emerged as a novel prognosticator in severe aortic stenosis (AS). However, its prognostic value in moderate AS has yet to be examined.

**Methods:** In this large retrospective multi-center study on patients with moderate AS, RV-PA coupling was first examined as a continuous variable, but to better understand the impact of each component of the ratio, RV-PA coupling was further defined as: (i) normal: normal pulmonary pressure (sPAP<35 mmHg); (ii) pulmonic phase: isolated pulmonary hypertension (sPAP≥35 mmHg and TAPSE≥18mm); (iii) RV phase: combination of pulmonary hypertension and RV dysfunction (sPAP≥35 mmHg and TAPSE<18mm). The cohort was further stratified according to these RV-PA coupling phases. Primary outcome was all-cause mortality at 5 years.

**Results:** A total of 1587 patients were included, of which 502 (32%) were classified in the pulmonic phase, 148 (9%) in the RV phase and 937 (59%) in the normal phase (Figure 1). Compared to the normal phase, patients in the pulmonic and RV phases had a higher prevalence of atrial fibrillation, increased prevalence of other valvular regurgitation, and larger left atrial volume index (all P<0.001). Patients in the RV phase showed more symptoms, and lower peak aortic valve velocity and left ventricular (LV) ejection fraction as compared to patients in the pulmonic or normal phase (both P<0.001). The Kaplan-Meier analysis revealed significant differences across the three phases overall and in pairwise comparisons (Figure 2). In multivariable analysis adjusting for age, sex, comorbidities, kidney function, symptoms, LV ejection fraction, E/e', valvular regurgitation, and aortic valve replacement (as a time dependent covariate), the pulmonic (hazard ratio [HR] 1.40, 95% confidence interval [CI] 1.12-1.74, P=0.003) and RV phases (HR 1.78, 95% CI 1.32-2.42, P<0.001) were independently associated with worse survival, with gradual increase in hazard ratio. When treating RV-PA coupling as a continuous variable, the restricted cubic spline showed a non-linear relationship with survival, and an optimal cutoff of 0.45 mm/mmHg was derived, which remained significantly associated with the outcome after adjusting for the same set of covariates (HR 1.71, 95% CI 1.35-2.16, P<0.001).

**Conclusion:** In moderate AS, RV-PA uncoupling is independently associated with worse survival and offers potential to enhance risk stratification and optimize management guidance.

	Normal (n=937)	Pulmonic phase (n=502)	RV phase (n=148)	Overall p
Age (mean (SD)), year	71.45 (12.12)	72.85 (11.33)	72.57 (10.46)	0.081
Male (%)	506 (54.0)	236 (47.0)*	77 (52.0)	0.041
BMI (mean (SD)), kg/m <sup>2</sup>	26.36 (6.13)	25.54 (5.38)*	25.17 (4.77)*	0.009
Obesity (%)	196 (21.2)	75 (15.5)*	18 (12.8)	0.005
Hypertension (%)	716 (76.6)	412 (82.4)*	118 (79.7)	0.035
Dyslipidemia (%)	680 (72.8)	378 (75.9)	120 (81.1)	0.070
Diabetes (%)	276 (29.5)	145 (29.0)	55 (37.2)	0.139
Coronary artery disease (%)	379 (40.5)	199 (39.7)	78 (52.7)*†	0.013
Atrial fibrillation (%)	218 (23.3)	180 (35.9)*	98 (66.2)*†	<0.001
Chronic lung disease (%)	68 (7.3)	37 (7.4)	10 (6.8)	0.965
Smoking (%)	312 (35.1)	116 (24.1)*	38 (26.8)	<0.001
NYHA II-IV	318 (34.5)	193 (38.8)	85 (57.4)*†	<0.001
Moderate TR (%)	13 (1.4)	38 (7.6)*	31 (20.9)*†	<0.001
Moderate or above MR (%)	59 (6.3)	78 (15.6)*	37 (25.0)*†	<0.001
LVEDD (mean (SD)), mm	47.36 (6.59)	48.56 (7.33)*	49.70 (8.19)*	<0.001
LV mass index (mean (SD)), g/m <sup>2</sup>	110.87 (31.81)	120.42 (37.44)*	125.89 (37.35)*	<0.001
Peak aortic valve velocity (mean (SD)), m/s	3.13 (0.55)	3.21 (0.52)*	2.81 (0.54)*†	<0.001
AVAI (mean (SD))	0.69 (0.12)	0.72 (0.12)*	0.72 (0.12)*	0.001
SV index (mean (SD)), ml/m <sup>2</sup>	48.53 (12.01)	51.65 (13.01)*	43.25 (12.59)*†	<0.001
LVEF (mean (SD)), %	58.73 (10.93)	57.88 (12.65)	46.83 (14.84)*†	<0.001
LAVI (mean (SD)), ml/m <sup>2</sup>	37.55 (18.25)	51.47 (27.48)*	63.42 (27.40)*†	<0.001
E/e' (mean (SD))	15.09 (7.95)	18.50 (10.23)*	20.27 (9.05)*	<0.001

\*P<0.05 vs. Normal. †P<0.05 vs. Pulmonic phase. AVAI = Aortic Valve Area Index; BMI = Body Mass Index; E/e' = E over e' prime ratio; LAVI = Left Atrial Volume Index; LVEDD = Left Ventricular End-Diastolic Diameter; LVEF = Left Ventricular Ejection Fraction; MR = Mitral Regurgitation; NYHA = New York Heart Association; SV = Stroke Volume; TR = Tricuspid Regurgitation.

