Circulation

ORIGINAL RESEARCH ARTICLE

mPAP/CO Slope and Oxygen Uptake Add Prognostic Value in Aortic Stenosis

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BACKGROUND: Recent guidelines redefined exercise pulmonary hypertension as a mean pulmonary artery pressure/cardiac output (mPAP/CO) slope >3 mm Hg·L^{-1}·min^{-1}. A peak systolic pulmonary artery pressure >60 mm Hg during exercise has been associated with an increased risk of cardiovascular death, heart failure rehospitalization, and aortic valve replacement in aortic valve stenosis. The prognostic value of the mPAP/CO slope in aortic valve stenosis remains unknown.

METHODS: In this prospective cohort study, consecutive patients (n=143; age, 73±11 years) with an aortic valve area ≤1.5 cm^2 underwent cardiopulmonary exercise testing with echocardiography. They were subsequently evaluated for the occurrence of cardiovascular events (ie, cardiovascular death, heart failure hospitalization, new-onset atrial fibrillation, and aortic valve replacement) during a follow-up period of 1 year. Findings were externally validated (validation cohort, n=141).

RESULTS: One cardiovascular death, 32 aortic valve replacements, 9 new-onset atrial fibrillation episodes, and 4 heart failure hospitalizations occurred in the derivation cohort, whereas 5 cardiovascular deaths, 32 aortic valve replacements, 1 new-onset atrial fibrillation episode, and 10 heart failure hospitalizations were observed in the validation cohort. Peak aortic velocity (odds ratio [OR] per SD, 1.48; *P*=0.036), indexed left atrial volume (OR per SD, 2.15; *P*=0.001), E/e' at rest (OR per SD, 1.61; *P*=0.012), mPAP/CO slope (OR per SD, 2.01; *P*=0.002), and age-, sex-, and height-based predicted peak exercise oxygen uptake (OR per SD, 0.59; *P*=0.007) were independently associated with cardiovascular events at 1 year, whereas peak systolic pulmonary artery pressure was not (OR per SD, 1.28; *P*=0.219). Peak Vo_2 (percent) and mPAP/CO slope provided incremental prognostic value in addition to indexed left atrial volume and aortic valve area (*P*<0.001). These results were confirmed in the validation cohort.

CONCLUSIONS: In moderate and severe aortic valve stenosis, mPAP/CO slope and percent-predicted peak Vo_2 were independent predictors of cardiovascular events, whereas peak systolic pulmonary artery pressure was not. In addition to aortic valve area and indexed left atrial volume, percent-predicted peak Vo_2 and mPAP/CO slope cumulatively improved risk stratification.

Key Words: aortic valve stenosis ■ cardiac output ■ exercise test ■ hypertension, pulmonary ■ prognosis

Pulmonary hypertension (PHT) portends a poor prognosis in aortic valve stenosis (AS).[1] Aside from AS severity, various myocardial and vascular maladaptations determine PHT, which can develop even before symptoms are reported.[2,3] Objectively adjudicating the cardiac origin of symptoms is particularly difficult in unfit or older individuals with multiple comorbidities. Timely detection of PHT in AS may enhance risk stratification

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.067130.
For Sources of Funding and Disclosures, see page 1181.

Circulation is available at www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- In patients with aortic stenosis and aortic valve area ≤1 cm² and no/equivocal symptoms or aortic valve area 1.0 to 1.5 cm² and symptoms, adverse cardiovascular events were independently predicted by the mean pulmonary artery pressure/cardiac output slope and age-, sex- and height-based predicted peak oxygen consumption (percent-predicted peak Vo_2).
- The mean pulmonary artery pressure/cardiac output slope was an independent predictor of outcome, whereas the peak systolic pulmonary artery pressure during exercise was not.
- Adding the mean pulmonary artery pressure/cardiac output slope and percent-predicted peak Vo_2 to aortic valve area improved risk stratification incrementally.

What Are the Clinical Implications?

- Combined exercise echocardiography and respiratory gas analysis provides prognostic information in patients with moderate or severe aortic stenosis and discordant symptoms.
- Patients with aortic valve area ≤1.5 cm² and cardiac limitation, defined by low percent-predicted peak Vo_2 in combination with high mean pulmonary artery pressure/cardiac output slope, should be monitored more closely and considered for potential aortic valve replacement.
- Assessment of exercise variables might enhance clinical decision-making on the timing of aortic valve replacement.

Nonstandard Abbreviations and Acronyms

AS	aortic valve stenosis
AVA	aortic valve area
AVR	aortic valve replacement
CO	cardiac output
CPETecho	cardiopulmonary exercise testing with echocardiography
exPHT	exercise-induced pulmonary hypertension
LAVi	indexed left atrial volume
mPAP	mean pulmonary artery pressure
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PHT	pulmonary hypertension
sPAP	systolic pulmonary artery pressure
TRG	tricuspid regurgitant gradient

and open a potential window for intervention to prevent further disease progression. However, early on, PHT might become apparent only during exercise (exPHT). Previously, Lancellotti et al[4] demonstrated that exPHT, defined by a peak systolic pulmonary artery pressure (sPAP) >60 mm Hg, was more prevalent than resting PHT in asymptomatic patients with severe AS and associated with reduced cardiac event-free survival.

Recently, the mean pulmonary artery pressure (mPAP)/cardiac output (CO) slope has been introduced to define exPHT.[5] The mPAP/CO slope during exercise incorporates the changes in mPAP and CO at rest and exercise. A higher slope has been associated with poor survival and cardiac events across multiple conditions. However, data on valvular heart disease are scarce.[6–9]

Although the prognostic value of peak exercise oxygen uptake (percent-predicted peak Vo_2) has been well established, the relevance of the mPAP/CO slope in AS has not yet been explored.[10,11] Therefore, this study aimed to evaluate the prognostic impact and additional value of exPHT, determined by the mPAP/CO slope, in patients with AS and aortic valve area (AVA) ≤1.5 cm².

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

Derivation Cohort

This prospective cohort study included consecutive patients with AVA ≤1.5 cm² and preserved left ventricular ejection fraction undergoing cardiopulmonary exercise testing with simultaneous echocardiography (CPETecho) for discordant symptoms between April 2016 and March 2022 as part of a standardized workup in a valvular heart disease clinic (Jessa Hospital, Hasselt, Belgium). Patients were followed up for 1 year for the occurrence of a prespecified composite outcome of cardiovascular death, heart failure hospitalization, new-onset atrial fibrillation, and aortic valve replacement (AVR). Indications for AVR are available in the Supplemental Methods S1. The study protocol was approved by the local ethical committees of Jessa Hospital and Hasselt University (Hasselt, Belgium; No. B2432020000038B).

Validation Cohort

We prospectively assessed for eligibility 220 consecutive patients with AVA ≤1.5 cm² and preserved ejection fraction who underwent CPETecho for discordant symptoms between September 2020 and January 2023 as part of a standardized workup in a valvular heart disease clinic (University Hospital of Pisa, Italy). Patients were followed up for the occurrence of the previously described composite outcome. The local ethics committee approved the protocol (No. 19204).

All study participants provided written informed consent before evaluation in the dyspnea clinic. All authors had full access to the data, took responsibility for the integrity of the

data, contributed to the manuscript, and agreed to this report as written.

Study Population

AS was defined by an AVA ≤1.5 cm^2, as recommended by current guidelines of the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[12,13] Symptoms were considered discordant when patients with severe AS (AVA ≤1.0 cm^2) had no or nonspecific symptoms or when patients with moderate AS (AVA, 1.0–1.5 cm^2) had symptoms (Supplemental Methods S2). The exclusion criteria were previous valve intervention, more than mild mitral stenosis/insufficiency or other moderate concomitant valve disease, and significant lung disease (Figure 1). To attenuate referral bias, patients with AVR within 3 months after CPETecho were excluded as well.

Cardiopulmonary Exercise Testing With Echocardiography

Respiratory Gas Analysis

The valvular heart disease clinic setup in Jessa Hospital has been described previously.[9,14] A similar protocol has been used in the University Hospital of Pisa.[15] All patients performed a standardized CPETecho protocol (Supplemental Methods S3). In summary, patients exercised on a semisupine bicycle ergometer (Cardiovit CS-200 Ergospiro, Schiller, Baar, Switzerland; and Ergoline ergoselect 1200 GmbH, Germany) with continuous 12-lead electrocardiographic monitoring, breath-by-breath respiratory gas analysis, and noninvasive blood pressure cuff measurements every 3 minutes. After a comprehensive transthoracic echocardiography at rest, a ramp protocol was initiated, aiming for 10 to 15 minutes of exercise. Intermediate exercise was defined by crossing the first ventilatory threshold as previously described.[14] Patients were encouraged to exercise until a respiratory exchange ratio ≥1.1 unless the early occurrence of limiting or high-risk signs or symptoms (ie, breathlessness, angina, fatigue, dizziness, significant repolarization abnormalities, complex ventricular arrhythmia, or a decrease in systolic blood pressure >20 mm Hg). Exercise capacity was assessed by the oxygen uptake during maximal effort (peak Vo_2), defined as the highest 20-second average of Vo_2 during exercise. Individual percent-predicted peak Vo_2 was calculated with the Wasserman and Hansen prediction equation: [(0.79×height)−60.7]×[50.72−(0.372×age)] if male or [(0.65×height)−42.8]+43×[22.78−(0.17×age)] if female.[16] The respiratory exchange ratio, oxygen pulse, and minute ventilation to carbon dioxide production slope were also collected.

Echocardiography

Experienced sonographers acquired 2-dimensional, Doppler, and tissue Doppler data sets in accordance with current guidelines using a Vivid E9 ultrasound machine (General Electric Healthcare, Chicago, IL) in Jessa Hospital and LISENDO 880 (Hitachi Medical Systems Tokyo, Japan) in Pisa.[12,13] The Devereux formula was used to calculate left ventricular mass index. Mitral annular early diastolic velocity (e') was measured at the septal annulus. Maximal left atrial volume was measured with the modified biplane Simpson method and indexed to body surface area (indexed left atrial volume [LAVi]). AVA was calculated by the continuity equation.[12,17] AS peak jet velocity (Vmax) was measured with continuous-wave Doppler ultrasound, using multiple acoustic windows to obtain the highest velocity. Mean pressure gradient was automatically calculated by averaging the instantaneous gradients over the ejection period. The sPAP at rest was determined from the maximal tricuspid regurgitant gradient (TRG), adding the estimated right atrial pressure from assessment of the inferior vena cava diameter and collapsibility.[13] For the sPAP during exercise, 10 mm Hg was added to the TRG as a fixed estimate of right atrial pressure.[4] PHT at resting conditions was defined by a tricuspid regurgitation velocity >2.8 m/s.[5] In Jessa Hospital, the tricuspid regurgitation envelope was enhanced by the routine administration of agitated

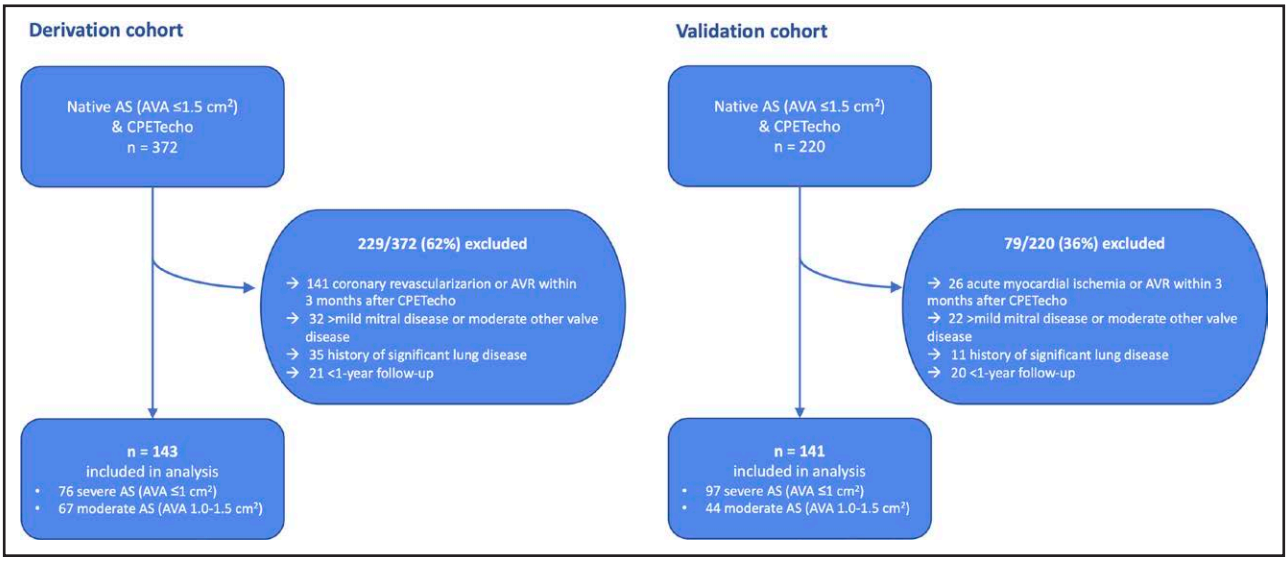

Figure 1. Study flowchart.
History of significant lung disease included chronic obstructive pulmonary disease with greater than Global Initiative For Obstructive Lung Disease classification II, interstitial lung disease, and previous lobectomy. AS indicates aortic valve stenosis; AVA, aortic valve area; AVR, aortic valve replacement; and CPETecho, cardiopulmonary exercise testing with simultaneous echocardiography.

colloid (Gelofusine 4%, Braun, Melsungen, Germany) at rest and intermediate and peak exercise to maximize feasibility and reproducibility, as previously described (Supplemental Methods S3; Figure S1).[18] The mPAP/CO slope was calculated by linear regression through 3 data points (mPAP and CO at rest and at intermediate and peak exercise; Supplemental Methods). mPAP was derived from the TRG without adding a right atrial pressure estimation using the Chemla formula.[19] CO was measured with the left ventricular outflow tract method. ExPHT was defined by an mPAP/CO slope >3 mm Hg·L^{-1}·min^{-1}.[5] Tricuspid annular plane systolic excursion/sPAP ratio was used to assess right ventricular–pulmonary arterial coupling.[20]

Event-Free Survival

Follow-up was obtained from patient records, interviews (with the next of kin if necessary), and their physicians. Adverse cardiovascular event was defined as cardiovascular death, heart failure hospitalization, new-onset atrial fibrillation, or AVR motivated by the development of symptoms or left ventricular systolic dysfunction.[3] Clinical management of the patient was independently determined by the patient's personal physician.

Statistical Analysis

Results are displayed as mean±SD or median (interquartile range) when distribution was not normal. The Shapiro-Wilk test was used to examine the normality of distribution. Categorical data are expressed as percentages and compared with the Fisher exact test. Independent predictors of outcome at follow-up were determined by logistic regression analysis based on the unmet assumption of proportional hazards over time. First, univariable analyses were performed on relevant covariables from the Lancellotti et al[4] pivotal article that evaluated the prognostic value of sPAP at peak exercise (peak sPAP) in AS. Tricuspid annular plane systolic excursion/sPAP was added to these univariable analyses because its prognostic importance has recently been demonstrated.[8] Three covariables with a univariable value of $P<0.1$ were integrated into the multivariable regression model by the entry method. To avoid overfitting the model, separate models were created to include the covariates of interest. Models were checked for collinearity by the variance inflation factors and compared with the likelihood ratio and χ^2 test. Cardiac event–free survival for mPAP/CO slope as a categorical variable (ie, presence or absence of exPHT) was obtained by Kaplan-Meier estimates and compared by a 2-sided log-rank test. A sensitivity analysis of this cardiac event–free survival was performed excluding AVR from the composite outcome (Figure S2).

The Pisa group agreed to test the prediction models derived in the Belgian cohort for external validation. The prediction accuracy of the validation cohort was demonstrated by applying the logistic regression coefficients for predicting events derived from the derivation cohort to the validation data set. Classification tables were used to evaluate the predictive accuracy of the logistic regression models derived from the derivation cohort, and the criterion value was applied, corresponding to the Youden index J derived from the receiver-operating characteristic curve analysis of the models in the derivation cohort. Two-tailed values of $P<0.05$ were considered significant. All statistics were performed with R studio version 1.4.1103 (RStudio PBC, Boston, MA) and Jamovi version 2.3 (The Jamovi project 2022, Computer Software).

RESULTS

Study Population

In Hasselt, 143 of 372 patients (38%) with AVA ≤1.5 cm^2, having had CPETecho for discordant symptoms, were eligible for the study, and in Pisa, 141 of 220 (64%; Figure 1) were eligible. In the derivation cohort, 76 patients (53%) had severe AS (AVA ≤1.0 cm^2) and 67 (47%) had moderate AS (AVA 1.0–1.5 cm^2). In the validation cohort, 97 patients (69%) had severe AS and 44 (31%) had moderate AS. In both cohorts, the population consisted mainly of male patients. Participants in the validation cohort were older (76±8 years of age versus 73±11 years of age in the derivation cohort), with similar sex distribution, body mass index, and body surface area (Table 1). Echocardiography diagnosed a bicuspid aortic valve in <10% of patients overall. Median NT-proBNP (N-terminal pro-B-type natriuretic peptide) was significantly higher in the validation group (n=424; 214–1069 ng/L) than in the derivation group (n=280; 110–790 ng/L).

Echocardiographic Characteristics

AS severity was similar in the derivation and validation cohorts (Table 2), with a similar proportion of low-flow, low-gradient AS (25% and 20%, respectively). Left ventricular internal diameters were higher in the validation cohort. Both cohorts showed a similar left ventricular systolic and diastolic function. Right ventricular function parameters and sPAP at rest were higher in the validation group.

During exercise, Vmax and mean gradient rose similarly in both cohorts, as pulmonary hemodynamics and CO-related parameters, except for a lower peak heart rate (percentage of estimated maximal heart rate) in the derivation cohort (Table 3). The mPAP/CO slope was similar in both cohorts (derivation, 4.1±2.7 mm Hg·L^{-1}·min^{-1}; validation, 4.0±2.6 mm Hg·L^{-1}·min^{-1}).

CPET Performance

CPET-derived parameters are shown in Table 3. Seventy-four patients (52%) achieved >80% of predicted peak Vo_2 in the derivation cohort and 61 (43%) in the validation cohort. Baseline characteristics of patients with high versus low (<80%) predicted peak Vo_2 are available in Tables S1 and S2.

Cardiac Events and Predictors of Outcome

In the derivation cohort, 46 patients (32%) reached the composite outcome at 1 year of follow-up, comprising 1

Table 1. Baseline Characteristics

Variables	Derivation cohort (Hasselt, n=143)	Validation cohort (Pisa, n=141)	*P* value
Demographics			
Age, y	73±11	76±8	0.022
Men, n (%)	98 (69)	83 (59)	0.084
BMI, kg/m^2	27±5	26±4	0.063
Bicuspid, n (%)	12 (9)	7 (5)	0.194
BSA, m^2	1.9±0.2	1.9±0.2	0.072
SBP, mm Hg	144±22	136±21	0.014
DBP, mm Hg	78±14	75±13	0.082
Heart rate at rest, bpm	68±12	71±12	0.067
Biochemical profile			
NT-proBNP, ng/L*	280 (110-790)	424 (214-1069)	0.010
Serum creatinine, mg/dL*	1.0 (0.8-1.2)	0.9 (0.8-1.2)	0.092
Hemoglobin, g/dL*	13±2	13±2	1.000
Comorbidities			
Hypertension, n (%)	78 (55)	104 (74)	0.001
Diabetes, n (%)	21 (15)	34 (24)	0.063
CAD, n (%)	42 (29)	28 (20)	0.087
History of AF, n (%)	32 (22)	40 (28)	0.247
Dyslipidemia, n (%)	110 (77)	97 (69)	0.134
Smoker, n (%)	65 (45)	32 (23)	0.001
Drugs			
Beta-blocker, n (%)	49 (37)	67 (48)	0.064
Loop diuretic, n (%)	20 (15)	41 (29)	0.011
SGLT2 inhibitor, n (%)	0 (0)	7 (5)	0.010
ACE or ARB, n (%)	65 (49)	94 (67)	0.017
MRA, n (%)	26 (19)	30 (21)	0.673

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AF, atrial fibrillation; BMI, body mass index; BSA, body surface area; CAD, coronary artery disease; DBP, diastolic blood pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; and SGLT2, sodium-glucose transporter-2.

*Fifty were missing data for NT-proBNP, 22 for serum creatinine, and 21 for hemoglobin in the derivation cohort.

Table 2. Echocardiographic Characteristics at Rest

Variables	Derivation cohort (Hasselt, n=143)	Validation cohort (Pisa, n=141)	*P* value
AS severity			
Vmax, m/s	3.4±0.7	3.7±0.9	0.061
MG, mm Hg	30±12	34±17	0.069
AVA, cm^2	1.0±0.2	0.9±0.3	0.083
AVA ≤1 cm^2, n (%)	76 (53)	90 (64)	0.063
AVAi, cm^2/m^2	0.5±0.1	0.5±0.2	0.999
SVi, mL/m^2	39±9	37±9	0.071
LVOTd, mm	21±2	20±3	0.064
Paradoxical LFLG severe AS, n (%)	36 (25)	28 (20)	0.310
Left ventricular dimensions			
IVS, mm	13±3	12±3	0.082
LVEDD, mm	45±7	49±8	0.035
PWT, mm	11±2	10±3	0.067
LVEDV, mL	104±36	118±45	0.013
LVESV, mL	45±21	51±29	0.060
LVMi, g/m^2	99±36	116±35	0.001
LAVi, mL/m^2	31±16	35±18	0.065
Left ventricular systolic and diastolic function			
LVEF, %	57 (53–60)	62 (58–68)	0.073
CO, L/min	4.9±1.2	5.0±1.5	0.549
E wave, cm/s	67±18	73±26	0.063
A wave, cm/s	80±24	88±30	0.067
E/A	0.8±0.4	0.9±0.6	0.097
Septal e', cm/s	4.9±1.4	5.3±1.5	0.062
Septal E/e'	13 (11-16)	13 (10-17)	0.584
RV function and hemodynamics			
S' RV, cm/s	9±3	10±4	0.032
TAPSE, mm*	17±5	20±3	0.001
Estimated RAP, mm Hg	3 (3-3)	3 (3-5)	0.286
TRV, m/s	2.4±0.3	2.7±0.6	0.025
sPAP, mm Hg	27±6	31±12	0.014
TAPSE/sPAP, mm/mm Hg*	0.65±0.24	0.61±0.22	0.192

AS indicates aortic valve stenosis; AVA, aortic valve area; AVAi, indexed aortic valve area; CO, cardiac output; IVS, interventricular septal thickness; LAVi, left atrial volume index; LFLG, low-flow, low-gradient; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVMi, left ventricular mass index; LVOTd, left ventricular outflow tract diameter; MG, mean gradient; PWT, posterior wall thickness; RAP, right atrial pressure; RV, right ventricular; sPAP, systolic pulmonary arterial pressure; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid valve regurgitation velocity; and Vmax, peak aortic transvalvular velocity.

*Twenty-one were missing data for TAPSE and TAPSE/sPAP.

cardiovascular death, 32 AVRs, 9 new-onset atrial fibrillation episodes, and 4 heart failure hospitalizations.

Patients with exPHT (n=89) compared with those without exPHT (n=54) had a lower event-free survival at 1 year (61% versus 84%; *P*=0.003; Figure 2). Among the 89 patients with an elevated mPAP/CO slope, 1 died of cardiovascular issues, 22 underwent AVR, 6 experienced atrial fibrillation, and 4 had a heart failure hospitalization as their first cardiovascular event within 1 year. Patients with exPHT also demonstrated more adverse left atrial and ventricular abnormalities (Table S3).

Vmax, E/e', LAVi, and mPAP/CO slope were significantly associated with 1-year outcome, whereas age, sex, left ventricular ejection fraction, and peak gradient over the aortic valve during exercise were not. Tricuspid annular plane systolic excursion/sPAP was also not predictive of outcome in univariable analysis (Table 4).

Vmax, E/e', and LAVi were included as covariables in a multivariable model, along with mPAP/CO slope, peak

Table 3. CPETecho Characteristics

Variables	Derivation cohort (Hasselt, n=143)	Validation cohort (Pisa, n=141)	*P* value
Aortic valve			
Vmax peak, m/s	4.1±0.7	4.3±0.9	0.061
MG peak, mm Hg	43±16	46±19	0.174
Δ MG, mm Hg	12±8	12±9	0.999
Pulmonary hemodynamics			
TAPSE peak, mm*	21±6	23±8	0.062
sPAP peak, mm Hg	62±10	59±15	0.065
TAPSE/sPAP peak, mm/mm Hg*	0.35±0.12	0.39±0.17	0.062
mPAP/CO slope, mm Hg·L^{-1}·min^{-1}	4.1±2.7	4.0±2.6	0.758
CO			
SV peak, mL	84±19	81±23	0.232
Heart rate peak, bpm	117±22	116±22	0.705
Peak heart rate, % of estimated heart rate maximum	63±24	71±21	0.019
CO peak, L/min	9.8±2.6	9.4±3.2	0.253
SBP peak, mm Hg	175±33	175±27	0.999
DBP peak, mm Hg	84±17	83±17	0.625
CPET performance			
FEV_1, L	2.2±0.7	2.1±0.8	0.264
FEV_1 predicted, %	86±22	86±19	0.999
FVC, L	2.8±0.9	2.7±1.1	0.407
Maximal RER	1.12±0.09	1.10±0.09	0.075
RER ≥1.05, n (%)	119 (84)	111 (79)	0.274
Peak Vo_2, mL·kg^{-1}·min^{-1}	16±5	15±4	0.093
Peak Vo_2, % predicted	81±21	77±19	0.117
Peak Vo_2 ≥80%, n (%)	74 (52)	61 (43)	0.133
$PETCO_2$ maximum, mm Hg	35±5	34±4	0.072
$EqCO_2$ minimal	30±5	30±7	0.999
VE/VCO_2 slope	30±5	34±7	0.001
VE maximum, L/min^{-1}	49±18	46±19	0.196
VT, L	1.6±0.6	1.5±0.7	0.225
VE/MVV	0.55±0.14	0.52±0.16	0.093
Watts	87±44	79±35	0.082

CO indicates cardiac output; CPET, cardiopulmonary exercise testing; DBP, diastolic blood pressure; $EqCO_2$, CO_2 equivalent; FEV, forced expiratory volume in 1 second; MG, mean gradient; mPAP, mean pulmonary arterial pressure; MVV, maximum voluntary ventilation; $PETCO_2$, end-tidal CO2 partial pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; sPAP, systolic pulmonary arterial pressure; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion; VE, minute ventilation; VE/VCO_2, minute ventilation to carbon dioxide production; Vo_2, oxygen uptake; Vmax, peak aortic transvalvular velocity; and VT, tidal volume.

*Fifty were missing data for TAPSE peak and 50 were missing data for TAPSE/sPAP peak in the derivation cohort.

sPAP, sPAP at intermediate exercise level (intermediate sPAP), or percent-predicted peak Vo_2. The mPAP/CO slope remained independently associated with outcomes (Table 4), whereas peak sPAP and likewise intermediate sPAP (at 40±25 W) did not (Tables S5 and S6). Percent-predicted peak Vo_2 was also independently associated with outcome in this model (including Vmax, E/e', and LAVi; Table 5). All models were negative for multicollinearity (variance inflation factors <5). The multivariable model with percent-predicted peak Vo_2 had the highest area under the curve (0.803) with to the model with mPAP/CO slope and peak sPAP (area under the curve, 0.771 and 0.754; *P*=0.380 and *P*=0.154, respectively; Tables 4 and 5).

The likelihood of the composite outcome increased with a higher mPAP/CO slope, regardless of percent-predicted peak Vo_2 and AVA (Figure 3).

Because both mPAP/CO slope and percent-predicted peak Vo_2 were independent predictors, the incremental prognostic value of mPAP/CO slope and percent-predicted peak Vo_2 over peak sPAP, LAVi, and AVA was evaluated (Figure 4). Subsequently adding the echocardiographic (mPAP/CO slope; χ^2=28.9; *P*<0.001) and respiratory gas (percent-predicted peak Vo_2; χ^2=34.1; *P*=0.020) analysis of CPETecho to conventionally used resting echocardiographic parameters (AVA and LAVi) resulted in a significant increase in the accuracy of the model.

Moreover, a univariable sensitivity analysis of mPAP/CO slope as a categorical variable (ie, presence or absence of exPHT), without AVR in the composite outcome, supported the lower event rate in patients without exPHT (*P*=0.030; Figure S2).

In the derivation cohort, a total of 27 events occurred among the 45 patients with both low peak oxygen uptake and mPAP/CO slope >3, including 1 cardiovascular death, 18 AVRs, 3 heart failure hospitalizations, and 5 new-onset atrial fibrillation episodes. In contrast, 19 events occurred in the group in whom either oxygen uptake or mPAP/CO slope was normal (Figure S3). Differences between both groups are shown in Table S11.

In the validation cohort, 48 patients (34%) reached the composite outcome at 1 year of follow-up: 5 cardiovascular deaths, 32 AVRs, 1 new-onset atrial fibrillation, and 10 heart failure hospitalizations. After 1 year of follow-up, patients with exPHT had a lower event-free survival than those without exPHT (55% versus 75%; *P*=0.002; Figure S4). The previously described 4 multivariable models showed results similar to those of the derivation cohort (Tables S7 through S10). The multivariable mPAP/CO slope model (with Vmax, E/e', and LAVi) had a prediction accuracy of 70.3%, whereas the prediction accuracy of the model including percent-predicted peak Vo_2 along with the same previous covariables was 72.6%. Prediction accuracy was determined by analysis of the logistic regression coefficients for predicting the composite outcome from the derivation data set in the validation cohort and subsequent evaluation of the observed and predicted values.

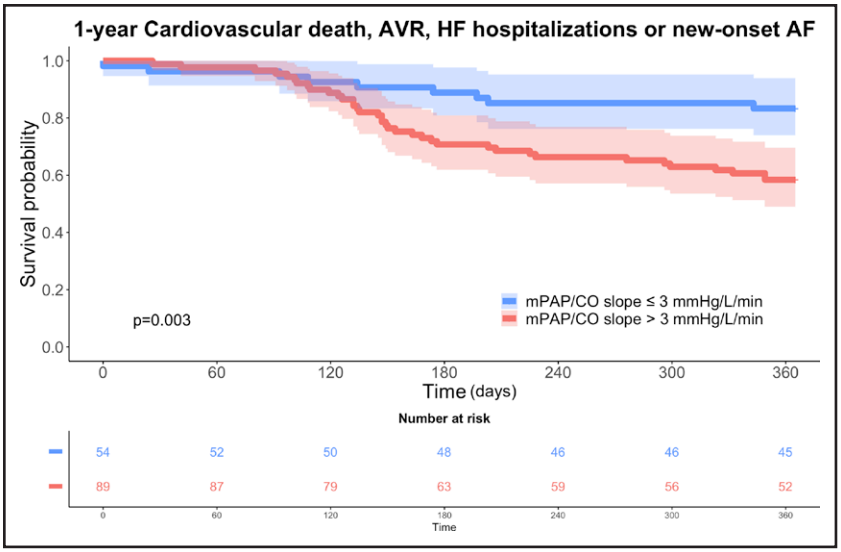

Figure 2. One-year survival curve for the composite outcome (cardiovascular death, HF hospitalization, new-onset AF, or AVR) according to mPAP/CO slope. Survival probability in mean pulmonary artery pressure/cardiac output (mPAP/CO) slope >3 mm Hg·L^{-1}·min^{-1} (red) and mPAP/CO slope ≤3 mm Hg·L^{-1}·min^{-1} (blue). Faded colors surrounding the survival curves indicate the CIs. Numbers at risk are displayed below the graph and colored according to their group. AF indicates atrial fibrillation; AVA, aortic valve area; AVR, aortic valve replacement; and HF, heart failure.

Finally, the combination of a low peak Vo_2 and exPHT yielded a lower event-free survival at 1 year compared with either a normal peak Vo_2 or the absence of exPHT (40% versus 82%, $P<0.001$; and 47% versus 77%, $P=0.001$, in the derivation and validation cohort, respectively).

DISCUSSION

The key findings of this study are as follows: (1) Both the mPAP/CO slope and percent-predicted peak Vo_2 are independently associated with adverse cardiovascular events in patients with AVA ≤1.5 cm^2 and discordant symptoms. (2) Both variables are more related to outcomes than peak exercise sPAP. (3) When added to AVA and LAVi at rest, the mPAP/CO slope and percent-predicted peak Vo_2 improved risk stratification.

exPHT in Past and Present Guidelines

PHT at rest is a marker of poor outcome, indicating an advanced and often irreversible stage of maladaptive

Table 4. Univariable Predictors and Multivariable Model for mPAP/CO Slope Predicting Adverse Cardiovascular Events in the Derivation Cohort

Model with mPAP/CO slope								
					Multivariable model for predicting adverse cardiovascular events			
Univariable predictors of adverse cardiovascular events					χ^2=25.4; AIC, 134; AUC, 0.771			
	OR per SD	β Value	AUC	*P* value	OR per SD	β value	*z* value	*P* value
Baseline characteristics								
Age	1.16 (0.81–1.68)	0.017	0.569	0.417				
Sex (reference: female)	0.90 (0.64–1.28)	−0.224	0.524	0.557				
Resting echocardiography								
Vmax	1.48 (1.03–2.12)	0.595	0.628	<0.050	1.73 (1.10–2.71)	0.842	2.40	<0.050
LVEF	0.85 (0.59–1.22)	−0.023	0.563	0.389				
E/e'	1.61 (1.11–2.32)	0.065	0.619	<0.050	1.06 (0.65–1.72)	0.006	0.19	0.809
LAVi	2.15 (1.37–3.37)	0.050	0.694	<0.050	1.86 (1.09–3.18)	0.041	2.36	<0.050
TAPSE/sPAP rest	0.99 (0.67–1.45)	−0.062	0.514	0.940				
CPETecho								
mPAP/CO slope	2.01 (1.29–3.12)	0.084	0.680	<0.050	1.63 (1.03–2.59)	0.183	2.10	<0.050
PG exercise	1.21 (0.85–1.73)	0.008	0.566	0.286				
TAPSE/sPAP peak	0.91 (0.59–1.42)	−0.733	0.550	0.689				

AIC indicates Akaike information criterion; AUC, area under the curve; CPETecho, cardiopulmonary exercise testing with echocardiography; LAVi, left atrial volume index; LVEF, left ventricular ejection fraction; mPAP/CO, mean pulmonary artery pressure/cardiac output; OR, odds ratio; PG, peak gradient; TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure; and Vmax, peak aortic transvalvular velocity.

Table 5. Univariable Predictors and Multivariable Model for Peak Vo_2 (Percent) Predicting Adverse Cardiovascular Events in the Derivation Cohort

Model with peak Vo_2, %								
Univariable predictors of adverse cardiovascular events					Multivariable model for predicting adverse cardiovascular events χ^2=31.1; AIC, 129; AUC, 0.803			
	OR per SD	β Value	AUC	*P* value	OR per SD	β value	*z* value	*P* value
Vmax	1.48 (1.03–2.12)	0.595	0.628	<0.050	1.92 (1.19–3.09)	1.002	2.70	<0.050
E/e'	1.61 (1.11–2.32)	0.065	0.619	<0.050	1.19 (0.74–1.93)	0.023	0.68	0.469
LAVi	2.15 (1.37–3.37)	0.050	0.694	<0.050	2.15 (1.25–3.70)	0.051	2.87	<0.050
Peak Vo_2, %	0.59 (0.40–0.86)	−0.026	0.636	<0.050	0.44 (0.26–0.75)	−0.040	−3.08	<0.050
Model with mPAP/CO slope vs model with peak Vo_2 (%)								<0.050

AIC indicates Akaike information criterion; AUC, area under the curve; LAVi, left atrial volume index; mPAP/CO, mean pulmonary artery pressure/cardiac output; OR, odds ratio; peak Vo_2, peak oxygen uptake (percent-predicted); and Vmax, peak aortic transvalvular velocity.

pulmonary vascular and cardiac remodeling in patients with AS.[1,2] Judging whether symptoms in daily life and even during exercise testing are proportional to exercise intensity is challenging, especially in older patients with comorbidities and multiple alternative causes of exercise intolerance.[15] Therefore, exPHT evaluation to identify failing cardiac reserve at an earlier stage is an appealing concept. Previously, more than half of asymptomatic patients with AS had exPHT, portending a poor prognosis.[4] Because of these data, a peak sPAP >60 mm Hg (or TRG >50) was included in previous guidelines to consider AVR but was excluded subsequently when more recent studies failed to confirm its value.[3,21]

Rationale for the Use of mPAP/CO Slope Rather Than Peak sPAP

The mPAP/CO slope could be more sensitive and specific than an absolute value of peak sPAP in evaluating exPHT for 3 main reasons. First, according to the Ohm law for fluid dynamics, total pulmonary artery pressures during exercise are related to pulmonary artery wedge pressure, pulmonary vascular resistance, and CO.[22,23] Current PHT guidelines recommend the mPAP/CO slope for evaluating the total pulmonary pressure during exercise with a cutoff of >3 mm Hg·L^{-1}·min^{-1} to define an abnormal response.[5] In fit patients with AS, the CO can be preserved, resulting in a peak sPAP >50 mm Hg but still a normal mPAP/CO slope. Second, a multipoint evaluation of exPHT is more feasible and reliable than a single sPAP at peak exercise, which was obtainable in some series in as few as only 41% of patients.[24–27] The feasibility and reliability can be even less if sPAP is evaluated after exercise or during upright (as opposed to semisupine) exercise.[25,26] The noninvasive mPAP/CO slope calculation has been validated against invasive exercise hemodynamics and is feasible in almost all patients when an agitated colloid is used for better TRG delineation.[28] Even when peak TRG is not obtainable with agitated colloid, the mPAP/CO slope can still be calculated by rest and intermediate exercise TRG and CO data points.

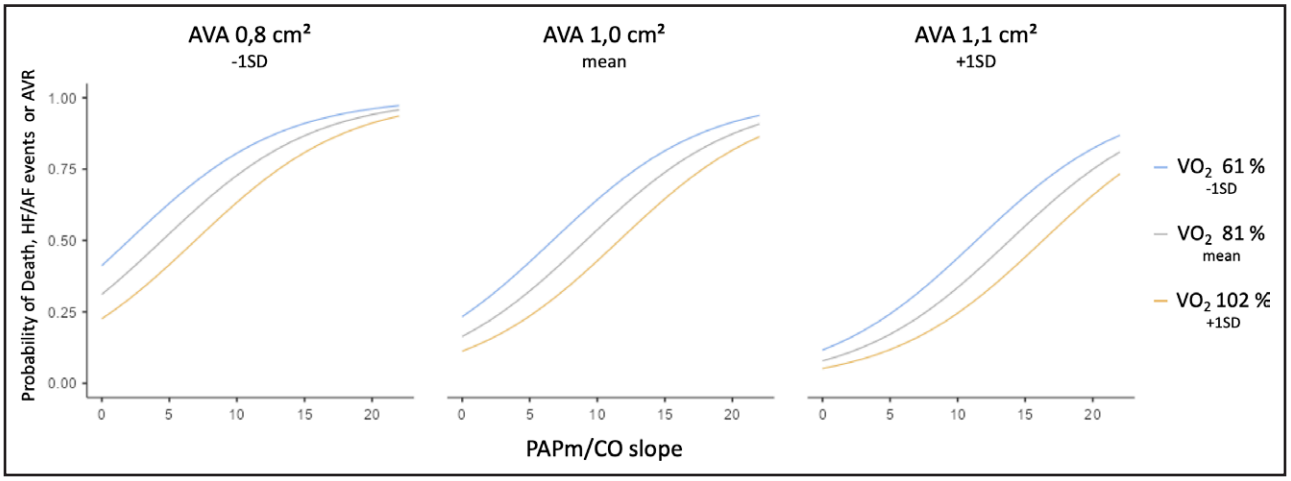

Figure 3. Probability of the composite outcome (cardiovascular death, HF hospitalization, new-onset AF or AVR) according to AVA, mPAP/CO slope, and percent-predicted peak Vo_2.
Estimated marginal means for 1-year outcome. AF indicates atrial fibrillation; AVA, aortic valve area; AVR, aortic valve replacement; HF, heart failure; mPAP/CO, mean pulmonary artery pressure/cardiac output and Vo_2, oxygen uptake.

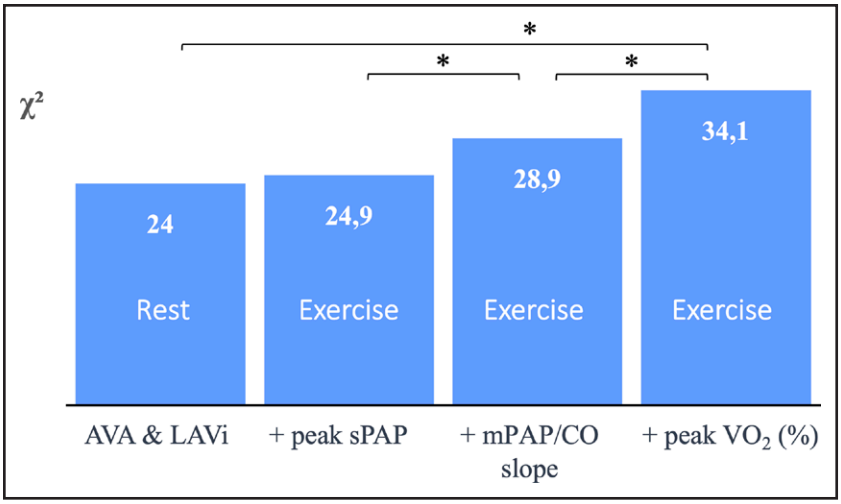

Figure 4. Additive value of mPAP/CO slope and percent-predicted peak Vo_2 to predict cardiovascular events in aortic stenosis.
The χ^2 distribution according to 4 models. Every bar, starting from **left** to **right**, adds the listed parameter to the previous model. The first bar indicates parameters at resting conditions; the other 3 add exercise parameters. AVA indicates aortic valve area; LAVi, left atrial volume index; mPAP/CO, mean pulmonary artery pressure/cardiac output; sPAP, systolic pulmonary artery pressure; and Vo_2, oxygen uptake. *$P<0.05$.

Arguments for Adding Exercise Capacity

Previous studies have shown that exercise capacity is often reduced in asymptomatic patients with AS, and peak Vo_2 was shown to predict outcomes more accurately than resting sPAP.[25,29] Workload during treadmill exercise echocardiography in asymptomatic severe AS was an independent predictor of events. However, these cutoff values do not apply to semisupine exercise.[25] In semisupine exercise testing, exercise capacity can be adequately evaluated only by peak Vo_2 using combined cardiopulmonary exercise testing because body position affects maximal workload, not peak Vo_2.[30] High pulmonary artery pressures relative to CO in combination with a low peak Vo_2 imply that the CO is insufficient to meet the muscle demands even at the cost of high filling pressures. Therefore, the low peak Vo_2 and high mPAP/CO combination could be considered the hallmark of cardiac limitation and an objective equivalent of symptoms. These findings are in line with what Coisne et al[31] showed for primary mitral regurgitation: Both TRG (+10 mm Hg for right atrial pressure) >55 mm Hg at 25 W during exercise echocardiography and a low peak Vo_2 (during a separate upright exercise test) predicted events and were complementary. It may seem easier to determine exercise TRG at a fixed load of 25 W. However, flow, not workload, determines the pulmonary pressure.[32] Moreover, a load of 25 W may signify minimal effort for one patient and maximal effort for another. It is noteworthy that sPAP at an intermediate exercise stage did not predict events in our cohort (Table S6).

Clinical Implications

ExPHT, defined by the mPAP/CO slope, and percent-predicted peak Vo_2 are independent predictors of cardiovascular events. The mPAP/CO slope and percent-predicted peak Vo_2 have incremental prognostic value over AS severity. CPETecho provides both percent-predicted peak Vo_2 and mPAP/CO slope in a single examination and may improve risk stratification and clinical decision-making in AS.[33] Assessing symptoms in older sedentary patients with AS is challenging. Thus, a patient with AS may be considered symptomatic when the peak Vo_2 is decreased in combination with the presence of exPHT. In addition, CPETecho can reveal noncardiac symptoms and limitations.[34] For instance, a low peak Vo_2 in the absence of exPHT could be caused by a diminished breathing reserve or a submaximal test, indicated by a low respiratory exchange ratio.[14,35] Patients with AS denying symptoms in daily life could be considered truly asymptomatic, particularly when they have a normal peak Vo_2 or low mPAP/CO slope.

Limitations

The derivation and validation cohorts were derived from a tertiary referral hospital; thus, there could be inherent flaws associated with selection and referral biases. As an observational study, this work cannot deduce causality. In the derivation cohort, a limited number of 46 total primary outcome events were available on which to model predictors. Nonetheless, all of the results were validated in an external cohort. The driver of the composite outcome was AVR in both the derivation and validation cohorts. Clinicians were not blinded and could have been biased by the results of the CPETecho, which could have resulted in more referrals for AVR. Most patients undergoing AVR had an mPAP/CO slope >3 mm Hg·L^{-1}·min^{-1}. Either referral bias or more advanced cardiac disease could be the reason. All patients receiving AVR within 3 months of CPETecho were excluded to minimize this inherent bias. The prognostic importance of CPETecho should be re-evaluated in a larger prospective multicenter study with only death or unplanned hospitalization as the outcome.

Conclusions

In AS with AVA ≤1.5 cm^2, mPAP/CO slope and percent-predicted peak Vo_2, evaluated simultaneously by CPETecho, were independent predictors of cardiovascular

events, whereas peak sPAP was not. In addition to conventional parameters of AS severity, both percent-predicted peak Vo_2 and mPAP/CO slope cumulatively improved risk stratification. These findings were confirmed in an independent validation cohort.

ARTICLE INFORMATION

Received September 14, 2023; accepted February 1, 2024.

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Acknowledgments

The authors thank the cardiology fellows who have contributed to performing the examinations in the dyspnea clinic of Jessa Hospital (Elise Bakelants, Ruben De Bosscher, Pieter-Jan Geselle, Siddharth Jogani, Kristof Lefebvre, Pieter Martens, Thibault Petit, Isabel Rooms, Martijn Scherrenberg, and Sarah Stroobants) and Pisa Hospital (Davide Maremmani, Francesco Filidei, Filippo Masi, Alessio Balletti, and Matteo Mazzola). They are grateful to Emila Guzzo, Lies Juwé, Daisy Thys, Kim Vanderhoydonck, Peter Vanvoorden, Dirk Verheyen, Kristien Wouters, and Silvia Armenia for their vital paramedic support in the clinic. They also thank Paolo Frumento for statistical support.

Sources of Funding

This research is partially funded by the Limburg Clinical Research Center of Hasselt University, Jessa and ZOL (Belgium; PhD grant), and the research cluster Centrum voor Hart-en Vaatziekten en Klinische Farmacie (CHVZ-KFAR), van de Vrije Universiteit Brussel. The research leading to these results has received funding from the European Union–NextGenerationEU through the Italian Ministry of University and Research under PNRR-M4C2-I1.3 project PE_00000019 "HEAL ITALIA" to Stefano Taddei, CUP I53C22001440006. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

Disclosures

None.

Supplemental Material

Methods S1–S3
Figures S1–S6
Tables S1–S11

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