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The mPAP/CO Slope and Oxygen Uptake

Add Prognostic Value in Aortic Stenosis

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Abstract

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

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

Results: One cardiovascular death, 32 AVRs, 9 new-onset AF episodes and 4 HF hospitalizations occurred in the derivation cohort, while 5 cardiovascular deaths, 32 AVRs, 1 new-onset AF episode and 10 HF hospitalizations were observed in the validation cohort. Peak aortic velocity (odds ratio per standard deviation (OR per SD), 1.48; p=0.036), indexed left atrial volume (LAVi; 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 (% predicted peak VO_2; OR per SD, 0.59; p=0.007) were independently associated with

cardiovascular events at 1 year, whereas peak sPAP was not (OR per SD, 1.28; p=0.219). Peak VO_2 (%) and mPAP/CO slope provided incremental prognostic value in addition to LAVi and AVA (p<0.001). These results were confirmed in the validation cohort.

Conclusion: In moderate and severe AS, mPAP/CO slope and % predicted peak VO_2 were independent predictors of cardiovascular events, while peak sPAP was not. In addition to AVA and LAVi, % predicted peak VO_2 and mPAP/CO slope cumulatively improved risk stratification.

Key Words

aortic valve stenosis; exercise testing; mPAP/CO; pulmonary hypertension; prognosis

Non-standard Abbreviations and Acronyms

- ACE: adverse cardiovascular events
- CPETecho: cardiopulmonary exercise testing with echocardiography
- exPHT: exercise induced pulmonary hypertension
- % predicted peak VO_2: % predicted peak oxygen consumption/aerobic capacity

Clinical Perspective

What is new?

- In patients with aortic stenosis (AS) and aortic valve area (AVA) ≤1 cm^2 and no/equivocal symptoms or AVA 1.0-1.5 cm^2 and symptoms, adverse cardiovascular events (ACE) were independently predicted by the mean pulmonary artery pressure/cardiac output (mPAP/CO) slope and age-, sex- and height-based predicted peak oxygen consumption (% predicted peak VO_2).
- The mPAP/CO slope was an independent predictor of outcome, whereas the peak systolic pulmonary artery pressure during exercise was not.
- Adding the mPAP/CO slope and % predicted peak VO_2 to AVA improved risk stratification incrementally.

What are the clinical implications?

- Combined exercise echocardiography and respiratory gas analysis (CPETecho) provides prognostic information in patients with moderate or severe AS and discordant symptoms.
- Patients with AVA ≤1.5 cm^2 and cardiac limitation, defined by low % predicted peak VO_2 in combination with high mPAP/CO slope, should be monitored more closely and considered for potential aortic valve replacement.
- Assessment of exercise variables might enhance clinical decision-making regarding the timing of aortic valve replacement.

Introduction

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 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. demonstrated that exPHT, defined by a peak systolic pulmonary artery pressure (sPAP) >60 mmHg, was more prevalent than resting PHT in asymptomatic patients with severe AS and associated with reduced cardiac event-free survival.(4)

Recently, the mean pulmonary artery pressure/cardiac output (mPAP/CO) slope has been introduced to define exPHT.(5) The mPAP/CO slope during exercise incorporates the changes in mean pulmonary artery pressure (mPAP) and cardiac output (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)

While the prognostic value of peak exercise oxygen uptake (% predicted peak VO_2) has been well established, the mPAP/CO slope's relevance 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 AVA ≤1.5 cm^2.

Methods

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

Study design

Derivation cohort

This prospective cohort study included consecutive patients with AVA ≤1.5 cm^2 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 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 Supplementary Methods S1. The study protocol was approved by the local ethical committees of Jessa Hospital and Hasselt University (Hasselt, Belgium; number B2432020000038B).

Validation cohort

We prospectively assessed for eligibility 220 consecutive patients with AVA ≤1.5 cm^2 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 (number 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 its integrity, contributed to the manuscript, and agreed to this report as written.

Study population

AS was defined by an aortic valve area (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 non-specific symptoms, or when patients with moderate AS (AVA 1.0-1.5 cm^2) had symptoms (Supplementary 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 (Hasselt, Belgium) has been described previously.(9, 14) A similar protocol has been used in the University Hospital of Pisa (Italy).(15) All patients performed a standardized CPETecho protocol (Supplementary Methods S3). In summary, patients exercised on a semi-supine bicycle ergometer (Cardiovit CS-200 Ergospiro,

Schiller, Baar, Switzerland and Ergoline ergoselect 1200 GmbH, Germany, respectively) with continuous 12-lead electrocardiography monitoring, breath-by-breath respiratory gas analysis, and non-invasive blood pressure cuff measurements every 3 min. After a comprehensive transthoracic echocardiography at rest, a ramp protocol was initiated, aiming for 10 to 15 mins 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 (i.e., breathlessness, angina, fatigue, dizziness, significant repolarization abnormalities, complex ventricular arrhythmia, or a decrease in systolic blood pressure >20 mmHg). 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 using Wasserman and Hansen's 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 was 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, United States) 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's 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 using 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 assessing the inferior vena cava diameter and collapsibility.(13) For the sPAP during exercise, 10 mmHg 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 colloid (Gelofusine 4%, Braun, Melsungen, Germany) at rest, intermediate and peak exercise to maximize feasibility and reproducibility, as previously described, (Supplementary Methods S3 & Figure S1).(18) The mPAP/CO slope was calculated by linear regression through 3 data points (mPAP and CO at rest, intermediate and peak exercise; Supplementary methods). The mPAP was derived from the TRG without adding a right atrial pressure estimation, using the Chemla formula.(19) The CO was measured with the left ventricular outflow tract method. ExPHT was defined by a mPAP/CO slope >3 mmHg/L/min.(5) Tricuspid annular plane systolic excursion (TAPSE)/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. ACE 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±standard deviation 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 using Fisher's 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 Lancellotti's pivotal paper that evaluated the prognostic value of sPAP at peak exercise (peak sPAP) in AS.(4) TAPSE/sPAP was added to these univariable analyses, as its prognostic importance has recently been demonstrated.(8) Three covariables with a univariable P-value<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 using the likelihood ratio and chi-square test. Cardiac event-free survival for mPAP/CO slope as a categorical variable (i.e. 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. (Supplementary 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 dataset. 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 ROC analysis of the models in the derivation cohort. Two-tailed P-values of <0.05 were considered significant. All statistics were performed using R studio version 1.4.1103 (RStudio PBC, Boston, United States) and Jamovi version 2.3 (The Jamovi project 2022, Computer Software).

Results

Study population

In Hasselt, 143 (38%) of 372 patients with AVA ≤1.5 cm^2, having performed CPETecho for discordant symptoms, were eligible for the study, and in Pisa, 141 of 220 (64%) (Figure 1). In the derivation cohort, 76 (53%) patients had severe AS (AVA ≤1.0 cm^2) and 67 (47%) moderate AS (AVA 1.0-1.5 cm^2). In the validation cohort, 97 (69%) patients 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 vs 73±11 years 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 N-terminal pro-B-type natriuretic peptide was significantly higher in the validation group (424, 214-1069 ng/L) than in the derivation group (280, 110-790 ng/L).

Echocardiographic characteristics

AS severity was similar in the derivation and validation cohort (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. RV 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 (% 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 mmHg/L/min; validation: 4.0±2.6 mmHg/L/min).

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 vs. low (<80%) predicted peak VO_2 are available in Supplementary Tables S1-2.

Cardiac events and predictors of outcome

In the derivation cohort, 46 (32%) patients reached the composite outcome at 1 year of follow-up, comprising one cardiovascular death, 32 AVRs, 9 new-onset atrial fibrillation episodes, and 4 heart failure hospitalizations.

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

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

Vmax, E/e' and LAVi, Vmax, LAVi were included as covariables in a multivariable model along with either mPAP/CO slope, peak sPAP, sPAP at intermediate exercise level (intermediate sPAP) or % predicted peak VO_2. The mPAP/CO slope remained independently associated with outcomes (Table 4) while peak sPAP, and likewise, intermediate sPAP (at 40±25 watts) did not (Supplementary Table S5-6). % 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 multi-collinearity (variance inflaction factors <5). The multivariable model with % predicted peak VO_2 had the highest area under the curve (AUC, 0.803) compared to the model with mPAP/CO slope and peak sPAP (AUC, 0.771 and AUC, 0.754, p=0.380 and p=0.154, respectively; Table 4 & 5).

The likelihood of the composite outcome increased with a higher mPAP/CO slope, irrespective of % predicted peak VO_2 and AVA (Figure 3).

Since both mPAP/CO slope and % predicted peak VO_2 were independent predictors, the incremental prognostic value of mPAP/CO slope and % predicted peak VO_2 over peak sPAP, LAVi and AVA was evaluated (Figure 4). Adding subsequently the echocardiographic (mPAP/CO slope; χ^2 28.9; p<0.001) and respiratory gas analysis (% predicted peak VO_2; χ^2 34.1; p=0.020) of CPETecho to conventionally used resting echocardiographic parameters (AVA and LAVi), resulted in a significant increase of the model's accuracy.

Moreover, a univariable sensitivity analysis of mPAP/CO slope as a categorical variable (i.e. presence or absence of exPHT), without AVR in the composite outcome, supported the lower event rate in patients without exPHT (p=0.030; Supplementary 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 AVR, 3 heart failure hospitalizations and 5 new-onset atrial fibrillation episodes. In contrast, 19 events occurred in the group where either oxygen uptake or mPAP/CO slope were normal (Supplementary Figure S3). Differences between both groups are shown in Supplementary Table S11.

In the validation cohort, 48 (34%) patients 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 follow-up, patients with exPHT had a lower event-free survival than those without exPHT (55% vs. 75%; p=0.002) (Supplementary Figure S4). The previously described four multivariable models showed similar results to the derivation cohort (Supplementary Table S7-10). The multivariable mPAP/CO slope model (with Vmax, E/e' and LAVi) had a prediction accuracy of 70.3%, while the prediction accuracy of the model including % predicted peak VO_2 along with the same previous covariables was 72.6%. Prediction accuracy was determined by analyzing the logistic regression coefficients for predicting the composite outcome from the derivation dataset in the validation cohort and subsequent evaluation of the observed and predicted values.

Finally, the combination of a low peak VO_2 and exPHT yielded a lower event-free survival at one year compared to either a normal peak VO_2 or the absence of exPHT (40% vs 82%, p<0.001 and 47% vs 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 % 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 the aortic valve area and LAVi at rest, the mPAP/CO slope and % predicted peak VO_2 improved risk stratification.

Exercise pulmonary hypertension in past and present guidelines

PHT at rest is a marker of poor outcome, indicating an advanced and often irreversible stage of maladaptive 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) Based on these data, a peak sPAP >60 (or TRG >50) mmHg was included in previous guidelines to consider AVR but excluded subsequently when more recent studies failed to confirm its value.(3, 21)

The 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 three main reasons. First, according to Ohm's 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 mmHg/L/min to define an abnormal response.(5) In fit patients with AS, the CO can be preserved, resulting in a peak sPAP >50 mmHg but still a normal mPAP/CO slope. Second, a multi-point evaluation of exPHT is more feasible and reliable than a single sPAP at peak exercise, which was obtainable in some series as few as only 41% of patients.(24-27) The feasibility and reliability can be even less if sPAP is evaluated postexercise or during upright (as opposed to semi-supine) exercise.(25, 26) The non-invasive mPAP/CO slope calculation has been validated against invasive

exercise hemodynamics and is feasible in almost all patients using agitated colloid 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.

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 don't apply to a semi-supine exercise.(25) In semi-supine exercise testing, exercise capacity can only be adequately evaluated by peak VO_2 using combined cardiopulmonary exercise testing since body position affects maximal workload and 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. showed for primary mitral regurgitation: both TRG (+10 mmHg for right atrial pressure) >55 mmHg at 25 Watt during exercise echocardiography and a low peak VO_2 (during a separate upright exercise test) predicted events and were complementary.(31) It may seem easier to determine exercise TRG at a fixed load of 25 watts. However, flow and not workload determines the pulmonary pressure.(32) Moreover, a load of 25 watts may signify a minimal effort for one patient and a maximal one for

another. Noteworthy, sPAP at an intermediate exercise stage did not predict events in our cohort (Supplementary Table S6).

Clinical implications

ExPHT, defined by the mPAP/CO slope, and % predicted peak VO_2 are independent predictors of cardiovascular events. The mPAP/CO slope and % predicted peak VO_2 have incremental prognostic value over aortic valve stenosis severity. CPETecho provides both % 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 sedentary, older 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. Additionally, CPETecho can reveal non-cardiac 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) AS patients 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 derive from a tertiary referral hospital; thus, there could be inherent flaws associated with selection and referral bias. As an observational study, we 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 a mPAP/CO slope >3 mmHg/L/min. 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 reevaluated in a larger prospective multicenter study with only death or unplanned hospitalization as the outcome.

Conclusion

In AS with AVA ≤1.5 cm^2, mPAP/CO slope and % predicted peak VO_2, evaluated simultaneously by CPETecho, were independent predictors of cardiovascular events, while peak sPAP was not. In addition to conventional parameters of AS severity, both % predicted peak VO_2 and mPAP/CO slope cumulatively improved risk stratification. These findings were confirmed in an independent validation cohort.

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Disclosures

The authors declare that there is no conflict of interest.

Supplemental Material

Methods S1 - 3

Figures S1 - 6

Tables S1 - 11

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Figure Legends

Figure 1: Study Flowchart.

History of significant lung disease included: chronic obstructive pulmonary disease with global initiative for obstructive lung disease (GOLD) classification >II, interstitial lung disease and previous lobectomy.

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 mPAP/CO slope >3 mmHg/L/min (in red) and mPAP/CO slope ≤3 mmHg/L/min (in blue). Faded colors surrounding the survival curves indicate the confidence intervals. The numbers at risk are displayed below the graph and colored according to their group.

AF, atrial fibrilliation; AVA, aortic valve area; AVR, aortic valve replacement; HF, heart failure.

Figure 3: Probability of the composite outcome (cardiovascular death, HF hospitalization, new-onset AF or AVR) according to AVA, mPAP/CO slope and % predicted peak VO_2.

Estimated marginal means for 1-year outcome.

Abbreviations as above; SD, standard deviation.

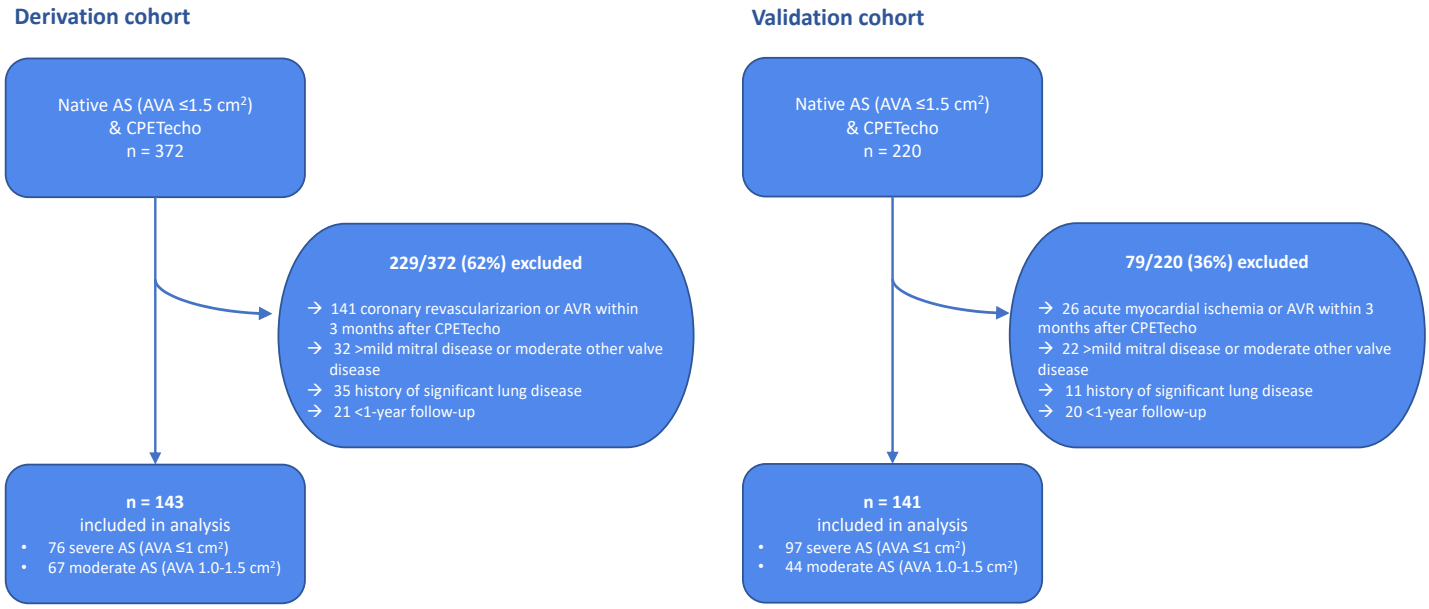
Figure 4: Additive value of mPAP/CO slope and % predicted peak VO_2 to predict cardiovascular events in aortic stenosis.

Chi square 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, while the other 3 add exercise parameters. * indicates a p-value <0.05.

LAVi, left atrial volume index; sPAP, systolic pulmonary artery pressure.

Figures

Figure 1



Tables

Table 1: Baseline characteristics

Variables	*Derivation cohort (Hasselt, n=143)*	*Validation cohort (Pisa, n=141)*	*P value*
Demographics			
Age (years)	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	1.86±0.2	0.072
SBP (mmHg)	144±22	136±21	**0.014**
DBP (mmHg)	78±14	75±13	0.082
Heart rate rest (bpm)	68±12	71±12	0.067
Biochemical profile			
NT-pro BNP (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 Mellitus, 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			
Betablocker, 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

** 50 missing data for NT pro BNP, 22 missing data for serum creatinine, 21 missing data 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***
Aortic stenosis severity			
Vmax (m/s)	3.4±0.7	3.7±0.9	0.061
MG (mmHg)	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 & 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
Right ventricular function & hemodynamics			
S' RV (cm/s)	9±3	10±4	**0.032**
TAPSE (mm)	17±5	20±3	**0.001**
Estimated RAP (mmHg)	3 (3-3)	3 (3-5)	0.286
TRV (m/s)	2.4±0.3	2.7±0.6	**0.025**
sPAP (mmHg)	27±6	31±12	**0.014**
TAPSE/sPAP (mm/mmHg)	0.65±0.24	0.61±0.22	0.192

AVA, aortic valve area; AVAi, indexed aortic valve area; IVS, interventricular septal thickness; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; IVRT, isovolumetric relaxation time; LFLG, low-flow, low-gradient; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; MG, mean gradient; PWT, posterior wall thickness; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SVi, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid valve regurgitation velocity; Vmax, peak aortic transvalvular velocity.

** 21 missing data for TAPSE and TAPSE/sPAP*

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 (mmHg)	43±16	46±19	0.174
delta MG (mmHg)	12±8	12±9	0.999
Pulmonary hemodynamics			
TAPSE peak (mm)	21±6	23±8	0.062
sPAP peak (mmHg)	62±10	59±15	0.065
TAPSE/sPAP peak (mm/mmHg)	0.35±0.12	0.39±0.17	0.062
mPAP/CO slope (mmHg/L/min)	4.1±2.7	4.0±2.6	0.758
Cardiac output			
SV peak (ml)	84±19	81±23	0.232
Heart rate peak (bpm)	117±22	116±22	0.705
Peak heart rate (% of estimated HR max)	63±24	71±21	**0.019**
CO peak (L/min)	9.8±2.6	9.4±3.2	0.253
SBP peak (mmHg)	175±33	175±27	0.999
DBP peak (mmHg)	84±17	83±17	0.625
CPET performance			
FEV1 (L)	2.2±0.7	2.1±0.8	0.264
FEV1 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/min)	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
$PETCO_2$ max (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 max (L)	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
Watt (watt)	87±44	79±35	0.082

CO, cardiac output; DBP, diastolic blood pressure; HR, heart rate; mPAP, mean pulmonary arterial pressure; RER, respiratory exchange ratio; sPAP, systolic pulmonary arterial pressure; SBP, systolic blood pressure; SV, stroke volume; VE/VCO2, minute ventilation to carbon dioxide production; VO_2, oxygen uptake; Vmax, peak aortic transvalvular velocity.

** 50 missing data for TAPSE peak, 50 missing data for TAPSE/sPAP peak in the derivation cohort.*

Figure 2

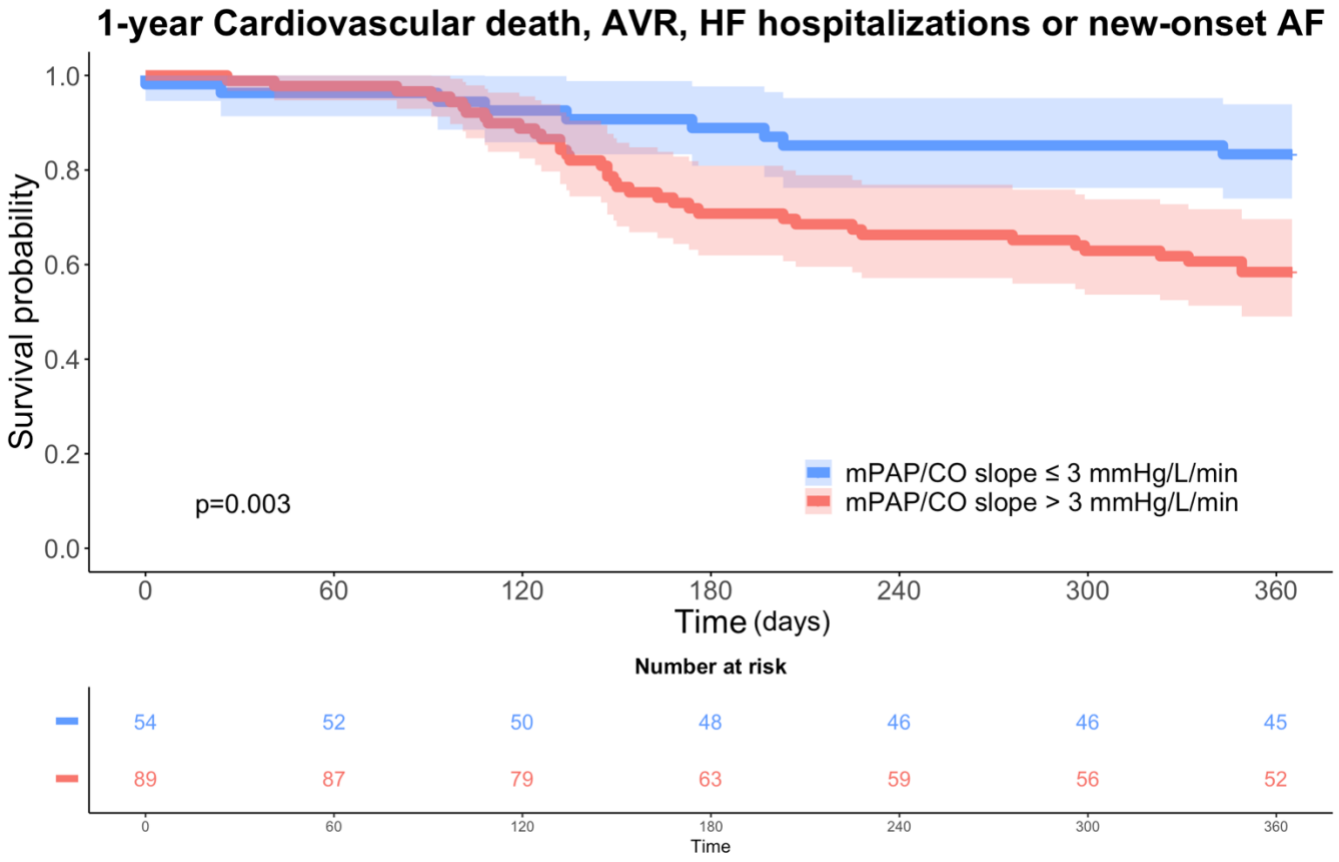

1-year Cardiovascular death, AVR, HF hospitalizations or new-onset AF
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
p=0.003
mPAP/CO slope ≤ 3 mmHg/L/min
mPAP/CO slope > 3 mmHg/L/min
0
60
120
180
240
300
360
Time (days)
Number at risk
54 52 50 48 46 46 45
89 87 79 63 59 56 52
0
60
120
180
240
300
360
Time

Figure 3

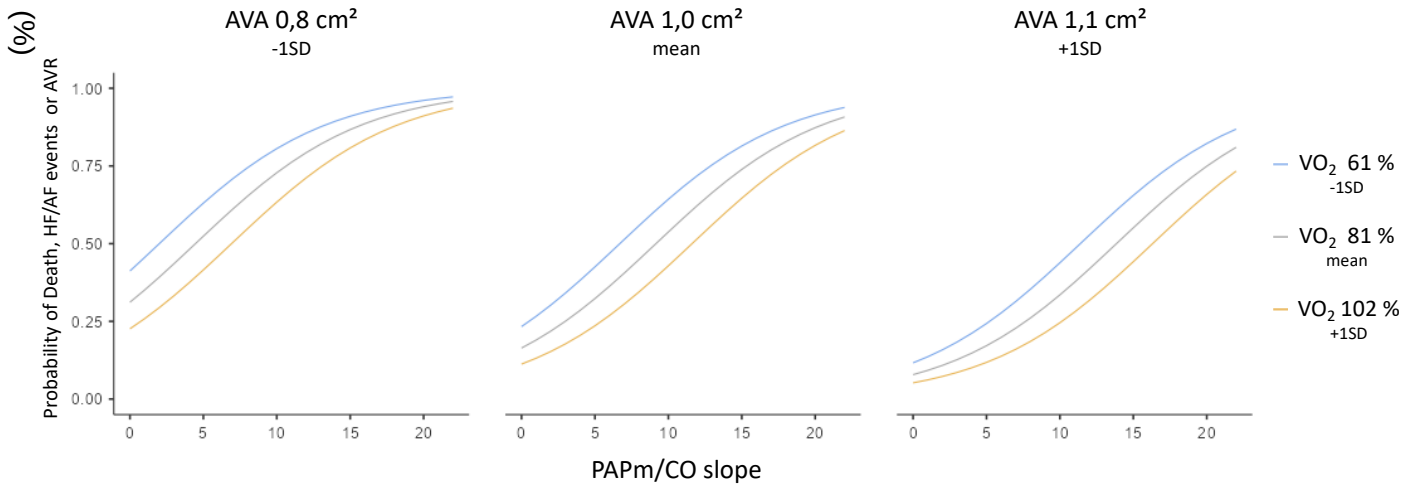

(%)
AVA 0,8 cm²
-1SD
AVA 1,0 cm²
mean
AVA 1,1 cm²
+1SD
Probability of Death, HF/AF events or AVR
1.00
0.75
0.50
0.25
0.00
0
5
10
15
20
PAPm/CO slope
VO2 61 %
-1SD
VO2 81 %
mean
VO2 102 %
+1SD

Table 4: Univariable predictors and multivariable model for mPAP/CO slope predicting ACE in the derivation cohort.

Model with mPAP/CO slope								
A. Univariable predictors of ACE					B. Multivariable model for predicting ACE			
					χ^2 25.4; AIC 134; AUC 0.771			
	OR per SD	β	AUC	p-value	OR per SD	β	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				
Cardiopulmonary exercise testing with Echocardiography								
mPAP/CO slope	2.01 (1.29–3.12)	0.084	0.680	<0.050	1.63 (1.03-2.59)	0.183	2.1	<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				

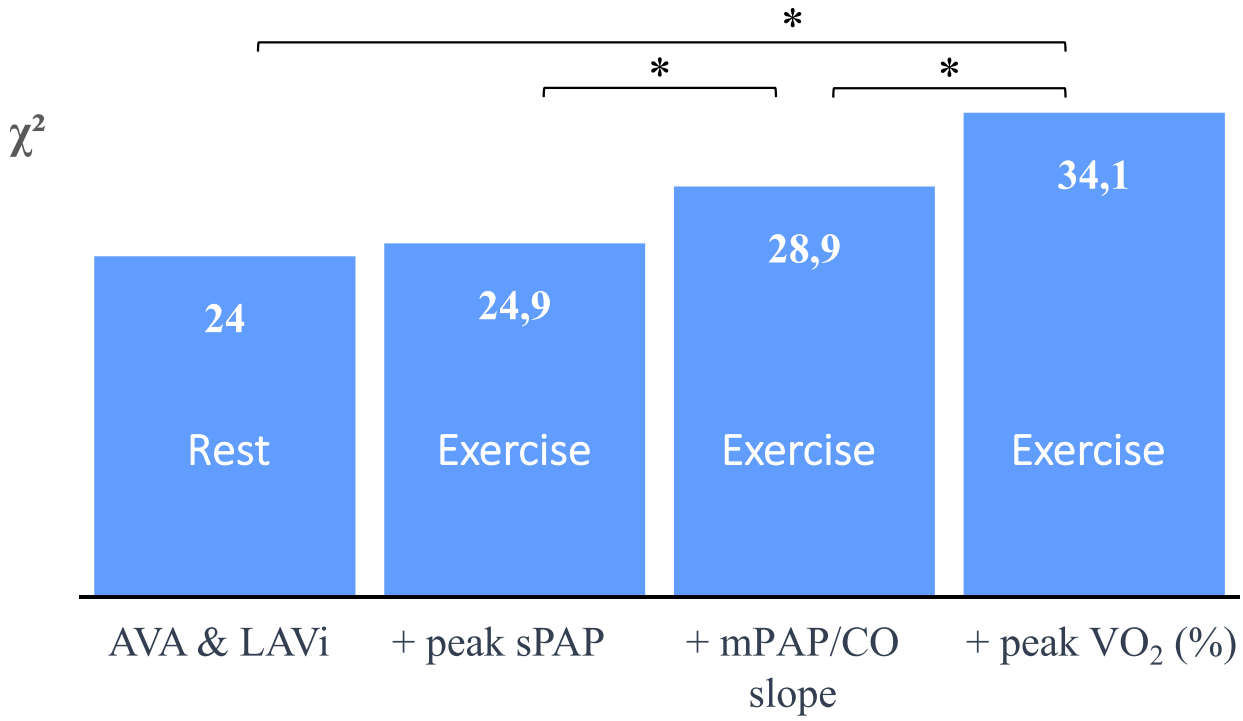
LAVi, left atrial volume index; LVEF, left ventricular ejection fraction, ACE, adverse cardiovascular events; mPAP/CO, mean pulmonary artery pressure/cardiac output; OR, odds ratio; PG, peak gradient; SD, standard deviation; TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure; Vmax, peak aortic transvalvular velocity.

Table 5: Univariable predictors and multivariable model for peak VO_2 (%) predicting ACE in the derivation cohort.

Model with peak VO_2 (%)								
A. Univariable predictors of ACE					B. Multivariable model for predicting ACE			
					χ^2 31.1; AIC 129; AUC 0.803			
	OR per SD	β	AUC	p-value	OR per SD	β	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 VO2 (%)								<0.050

Peak VO_2 (%), peak oxygen uptake (% of predicted).

Figure 4


*
*
*
χ²
24
Rest
24,9
Exercise
28,9
Exercise
34,1
Exercise
AVA & LAVi
+ peak sPAP
+ mPAP/CO slope
+ peak VO2 (%)