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**ORIGINAL PAPER**

# Cardiac dysfunction rather than aortic valve stenosis severity drives exercise intolerance and adverse haemodynamics

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**See the editorial comment for this article 'Heart failure with preserved ejection fraction in patients with moderate/severe aortic stenosis: what harms our patients most?', by M.W. Bergmann, https://doi.org/10.1093/ehjci/jead329.**

**Aims** To study the impact of heart failure with preserved ejection fraction (HFpEF) vs. aortic stenosis (AS) lesion severity on left ventricular (LV) hypertrophy, diastolic dysfunction, left atrial (LA) dysfunction, haemodynamics, and exercise capacity.

**Methods and results** Patients ($n = 206$) with at least moderate AS (aortic valve area $\leq 0.85$ cm/m$^2$) and discordant symptoms underwent cardiopulmonary exercise testing with simultaneous echocardiography. The population was stratified according to the probability of underlying HFpEF by the heavy, hypertension, atrial fibrillation, pulmonary hypertension, elder, filling pressure ($H_2$FPEF) score [0–5 (AS/HFpEF–) vs. 6–9 points (AS/HFpEF+)] and AS severity (Moderate vs. Severe). Mean age was 73 ± 10 years with 40% women. Twenty-eight patients had Severe AS/HFpEF+ (14%), 111 Severe AS/HFpEF– (54%), 13 Moderate AS/HFpEF+ (6%), and 54 Moderate AS/HFpEF– (26%). AS/HFpEF+ vs. AS/HFpEF– patients, irrespective of AS severity, had a lower LV global longitudinal strain, impaired diastolic function, reduced LV compliance, and more pronounced LA dysfunction. The pulmonary arterial pressure–cardiac output slope was significantly higher in AS/HFpEF+ vs. AS/HFpEF– (5.4 ± 3.1 vs. 3.9 ± 2.2 mmHg/L/min, respectively; $P = 0.003$), mainly driven by impaired cardiac output and chronotropic reserve, with signs of right ventricular pulmonary arterial uncoupling. AS/HFpEF+ vs. AS/HFpEF– was associated with a lower peak aerobic capacity (11.5 ± 3.7 vs. 15.9 ± 5.9 mL/min/kg, respectively; $P < 0.0001$) but did not differ between Moderate and Severe AS (14.7 ± 5.5 vs. 15.2 ± 5.9 mL/min/kg, respectively; $P = 0.6$).

**Conclusion** A high $H_2$FPEF score is associated with a reduced exercise capacity and adverse haemodynamics in patients with moderate to severe AS. Both exercise performance and haemodynamics correspond better with intrinsic cardiac dysfunction than AS severity.

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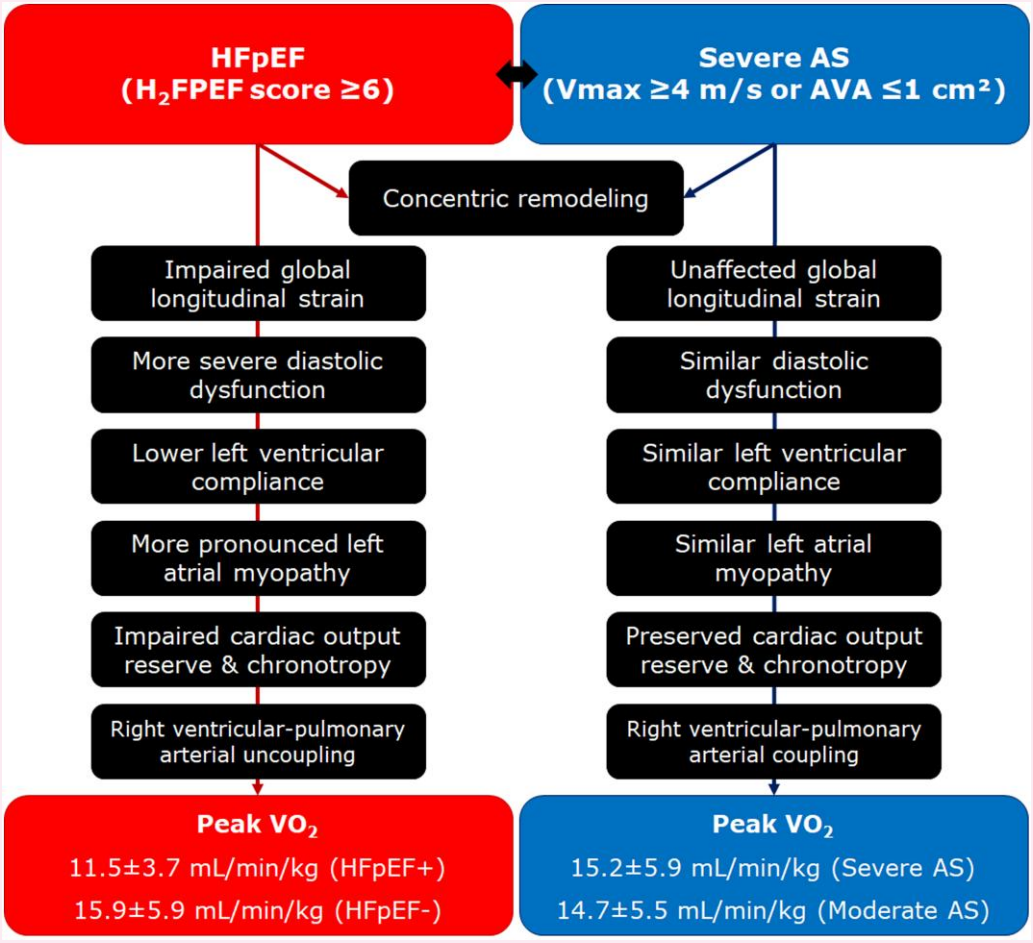
## Graphical Abstract




AS, aortic valve stenosis; HFpEF, heart failure with preserved ejection fraction; $VO_2$, aerobic capacity; *$P < 0.001$.

**Keywords** aortic valve stenosis • diastolic heart failure • exercise test • heart atria • haemodynamics

# Introduction

Both heart failure with preserved ejection fraction (HFpEF) and aortic stenosis (AS) present with left ventricular (LV) hypertrophy, diastolic dysfunction, left atrial (LA) dysfunction, and eventually pulmonary hypertension, but their overlap is poorly understood.[1–3] Current staging systems for cardiac dysfunction in AS assume that all pathology is due to the valve lesion, yet on an individual patient level, the myocardial response may be very heterogeneous and is likely driven by co-morbid conditions and age as well.[4,5] In patients undergoing aortic valve replacement, the extent of extra-valvular cardiac damage and its reversibility after intervention have important prognostic implications.[6–9] More insight is needed on the causality between AS lesion severity and extra-valvular cardiac damage.

The heavy, hypertension, atrial fibrillation, pulmonary hypertension, elder, filling pressure ($H_2$FPEF) score provides a robust means of estimating the probability that underlying HFpEF is present.[10] The score, which is determined in large part (i.e. 7 of the total of 9 points) by HFpEF risk factors (i.e. obesity, hypertension, atrial fibrillation, and age) rather than cardiac filling pressures *per se*, independently predicts cardiac dysfunction, haemodynamic abnormalities, impairments in functional capacity, and an increased risk of events in patients with HFpEF, in patients without cardiac disease and importantly in patients with AS after transcatheter aortic valve implantation.[11–14] Higher $H_2$FPEF scores were associated with an increased presence of paradoxical low-flow, low-gradient severe AS, presumably by identifying a population with more intrinsic myocardial disease.[13] We hypothesized that patients with moderate to severe AS and a high probability of HFpEF estimated by the $H_2$FPEF score would display poorer cardiac function, exertional haemodynamics, and aerobic capacity as compared to patients with similar AS severity and low HFpEF probability.

# Methods

## Study design

This prospective, observational cohort study includes consecutive patients with moderate symptomatic or severe asymptomatic AS, referred for cardiopulmonary exercise testing with simultaneous echocardiography (CPETecho) to a single tertiary care valve clinic (Jessa Hospital, Hasselt, Belgium) between October 2016 and December 2021. All subjects underwent the same standardized CPETecho protocol (see Supplementary data

| | Clinical Variable | Values | Points |
|---|---|---|---|
| $H_2$ | Heavy | Body mass index > 30 kg/m$^2$ | 2 |
| | Hypertensive | 2 or more antihypertensive medicines | 1 |
| F | Atrial Fibrillation | Paroxysmal or Persistent | 3 |
| P | Pulmonary Hypertension | Doppler Echocardiographic estimated Pulmonary Artery Systolic Pressure > 35 mmHg | 1 |
| E | Elder | Age > 60 years | 1 |
| F | Filling Pressure | Doppler Echocardiographic E/e' > 9 | 1 |
| $H_2$FPEF score | | | Sum (0-9) |

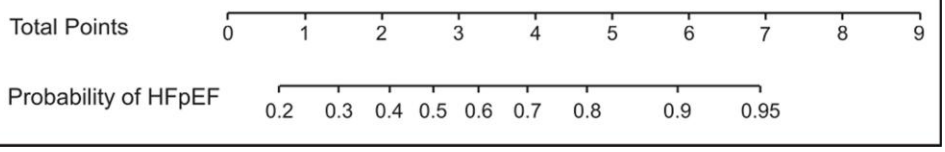



**Figure 1** Detailed breakdown of the $H_2$FPEF score. Reproduced from Reddy et al.[10] with permission.

online, *Supplementary Methods*). In brief, we did a comprehensive transthoracic echocardiography on a semi-supine bicycle ergometer (Cardiovit CS-200 Ergospiro, Schiller, Baar, Switzerland) with continuous 12-lead electrocardiography monitoring, breath-by-breath respiratory gas analysis, and non-invasive blood pressure cuff measurements every 3 min. After acquiring a complete set of echo images at rest, subjects conducted a continuous ramp protocol tailored to achieve 10–15 min of exercise. The ramp was halted twice: (i) around the first ventilatory threshold or earlier if needed to ensure a heart rate of <100 bpm (to allow diastolic stress testing with separated E and A waves on the transmitral pulsed-wave Doppler) and (ii) close to peak exertion, to enable the acquisition of a set of echo images at submaximal and maximal exercise. We encouraged patients to continue 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). The local ethical committees of Jessa Hospital and Hasselt University (Hasselt, Belgium) approved the study. All authors had full access to the data, take responsibility for its integrity, contributed to the manuscript writing, and agree to this report as written.

## Study population

Patients with at least moderate AS, defined by an indexed aortic valve area (AVAi) ≤0.85 cm$^2$/m$^2$ measured at rest, referred for CPETecho because of discordant symptoms, were included. Patients referred with severe AS were considered to be asymptomatic by their treating physicians, and the goal was to identify symptoms or objective functional impairment to establish an indication for aortic valve replacement. Alternatively, symptomatic patients with moderate AS were referred to exclude a severe dynamic lesion. AVAi was determined by the continuity equation in compliance with current guidelines by the European Association of Cardiovascular Imaging and the American Society of Echocardiography.[15,16] Exclusion criteria were a previous valve intervention, more than mild mitral valve stenosis, more than moderate other concomitant valve disease, a LV ejection fraction <50%, coronary revascularization within 3 months after CPETecho, and a history of significant lung disease. Significant underlying coronary artery disease was excluded by either a coronary angiogram or coronary computed tomography in all patients.

## Population stratification

Patients were stratified according to AS severity and $H_2$FPEF score. Severe AS was defined as a peak jet velocity (Vmax) ≥4 m/s at rest or during exercise, while the remaining lesions were classified as moderate AS. A sensitivity analysis was performed with severe AS defined as an aortic valve area (AVA) ≤1 cm$^2$ measured at rest to account for patients with paradoxical low-flow, low-gradient severe AS and those with elevated Vmax during exercise because of high-flow despite normal AVA >1 cm$^2$. Patients with a $H_2$FPEF score 6–9, roughly corresponding to a >90% probability of underlying HFpEF, were considered to have a high likelihood of HFpEF.[10] Patients with a score 0–5 had a moderately low likelihood of HFpEF. A complete breakdown of the $H_2$FPEF score is provided as *Figure 1*. Hence, four groups were defined: (i) severe AS with a high likelihood of HFpEF (i.e. severe AS/HFpEF+); (ii) severe AS with a moderately low likelihood of HFpEF (i.e. severe AS/HFpEF−); (iii) moderate AS with a high likelihood of HFpEF (i.e. moderate AS/HFpEF+); and (iv) moderate AS with a moderately low likelihood of HFpEF (i.e. moderate AS/HFpEF−).

## Echocardiography measurements

Experienced sonographers used a Vivid E9 ultrasound machine (General Electric Healthcare, Chicago, IL, USA) to perform 2D Doppler, tissue Doppler, and speckle-tracking ultrasound examination in accordance with the current guidelines.[15,17] The Devereux formula was used to calculate LV mass index. Mitral annular early diastolic velocity (e') was measured at the septal annulus to calculate the $H_2$FPEF score, as was done for its

validation.[10] Maximal LA volume was measured with the modified biplane Simpson's method and indexed to body surface area. Deformation measurements were performed offline with EchoPAC (V.203, General Electric Healthcare, Chicago, IL, USA). LV global longitudinal strain was averaged from the apical four-, two-, and three-chamber view. LA strain was measured in the apical four-chamber view and is reported separately for reservoir, conduit, and contraction phases, with the zero-strain reference set at LV end-diastole. LA compliance was assessed by the ratio of LA reservoir strain over E/e′.[18] The diastolic stiffness constant (β) was calculated by the single-beat approach, as described by Klotz *et al.*[19,20] The LV end-diastolic pressure–volume relationships (LVEDPVR) were created from a single pressure–volume point by estimating β and a curve fitting constant (α), based on the premise that volume-normalized EDPVRs share a common shape. LV end-diastolic pressure (mmHg) was estimated as $11.96 + 0.596 \times E/e'$, which has been validated against invasive measurements.[21] The systolic pulmonary arterial pressure was determined from the maximal tricuspid regurgitant gradient, adding the estimated right atrial pressure from assessment of the inferior vena cava.[17] During exercise, 10 mmHg was added as a tentative estimate for right atrial pressure. Visualization of the tricuspid regurgitation envelope was enhanced by systematic administration of agitated colloid (Gelofusine 4%, Braun, Melsungen, Germany) at the end of image acquisition during all three stages of CPETecho (see Supplementary data online, *Supplementary Methods* and *Figure S1*). The mean pulmonary arterial pressure–cardiac output (mPAP/CO) slope was calculated for every individual subject. mPAP at each stage was derived from the maximal tricuspid regurgitant gradient without adding a right atrial pressure estimation, using the Chemla formula.[22] CO at each stage was measured with the LV outflow tract method. Tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure ratio was used to assess right ventricular (RV)–pulmonary arterial coupling.[23]

### Exercise capacity assessment

Exercise capacity was assessed by the peak aerobic capacity during maximal effort exertion (peak $VO_2$), defined as the highest 20-s average of $VO_2$ during exercise. The respiratory exchange ratio, oxygen pulse, minute ventilation to carbon dioxide production slope, and delta $VO_2$ over delta power ($\Delta VO_2/\Delta W$) ratio were also collected.

### Statistical analysis

Continuous variables are expressed as mean ± standard deviation or median (interquartile range) when not normally distributed and compared using the independent samples Student's *t*-test or Mann–Whitney *U* test as appropriate. Categorical data are expressed as percentages and compared with Fisher's exact test. The mPAP/CO slope was compared between groups using one-way analysis of covariance. Significance was set at a two-tailed probability level of <0.05. All statistics were performed using R studio version 1.4.1103 (RStudio PBC, Boston, MA, USA).

# Results

## Study population

A study flowchart is provided in *Figure 2* (see Supplementary data online, *Figure S2* for the sensitivity analysis according to AVA). From a total of 386 patients with moderate to severe AS, consecutively undergoing CPETecho in Jessa Hospital during the study period, 206 (53%) fulfilled all inclusion/exclusion criteria. The mean age was 73 ± 10 years with 83 women (40%). A bicuspid aortic valve according to echocardiographic assessment was present in 28 patients (14%). Stratification yielded 28 severe AS/HFpEF+ (14%), 111 severe AS/HFpEF− (54%), 13 moderate AS/HFpEF+ (6%), and 54 moderate AS/HFpEF− patients (26%). The distributions of the $H_2$FPEF score in moderate vs. severe AS are shown in Supplementary data online, *Figure S3*). Baseline characteristics according to the four study groups are presented in *Table 1*. AS/HFpEF+ vs. AS/HFpEF− patients had higher levels of *n*-terminal pro-hormone B-type natriuretic peptide, worse renal function, lower haemoglobin, and used loop diuretics more often. Patients with severe vs. moderate AS also had higher N-terminal pro-hormone B-type natriuretic peptide levels, more diabetes but less coronary artery disease, and used mineralocorticoid receptor antagonists less frequently.

## Aortic valve stenosis severity

Peak aortic jet velocity, mean gradient, AVA, and AVAi were similar between AS/HFpEF+ and AS/HFpEF− patients (see Supplementary data online, *Table S1*). Thirty-six patients had paradoxical low-flow, low-gradient severe AS (AVA ≤1 $cm^2$ with Vmax <4 m/s and stroke volume index ≤35 $mL/m^2$), who were evenly distributed among $H_2$FPEF strata. During each level of exercise, the peak aortic valve velocity and mean aortic gradient remained similar between AS/HFpEF+ and AS/HFpEF− patients, although the latter group had a significantly greater increase in the mean aortic gradient from rest to peak exercise (+10 ± 7 mmHg vs. +14 ± 10 mmHg, respectively; $P = 0.03$; *Table 2*).

## Cardiac morphology

Both AS/HFpEF+ patients and patients with severe AS (vs. AS/HFpEF− patients and patients with moderate AS, respectively) demonstrated concentric remodelling (see Supplementary data online, *Table S1*).

## LV systolic function at rest

While LV global longitudinal strain was very similar in patients with severe and moderate AS (16.4 ± 3.8% vs. 16.7 ± 3.4%, respectively; $P = 0.6$), it was significantly decreased in AS/HFpEF+ compared with AS/HFpEF− patients (15.4 ± 3.5% vs. 16.8 ± 3.7%, respectively; $P = 0.03$). Stroke volume was higher in the severe compared with moderate AS group when defined by Vmax, but the reverse was true with a lower stroke volume in the sensitivity analysis where severe AS was determined by AVA.

## LV diastolic function at rest

LV diastolic function parameters did not differ between moderate and severe AS at rest. In contrast, a high $H_2$FPEF score identified patients with a higher E-wave, E/A ratio, and E/e′ ratio, with the latter being a component of the score (see Supplementary data online, *Table S1*). A-wave duration was prolonged in AS/HFpEF+ patients. The LVEDPVR showed a leftwards and upwards shift in AS/HFpEF+ compared with AS/HFpEF− patients, indicating decreased LV compliance (*Figure 3A*). In contrast, severe AS was associated with a lower LV operational stiffness than moderate AS (*Figure 3B*).

## LA function at rest

AS/HFpEF+ patients had larger left atria than AS/HFpEF− patients, with reduced LA reservoir strain (19 ± 8% vs. 24 ± 8%; $P = 0.002$), along with reduced booster pump strain (12 ± 6% vs. 15 ± 5%; $P = 0.004$) with similar conduit strain (9 ± 5% vs. 9 ± 5%; $P = 0.9$; Supplementary data online, *Table S1*; *Figure 4*). LA reservoir strain over E/e′ ratio indicated a decreased LA compliance in AS/HFpEF+ patients. Neither LA size nor LA function was significantly different between severe and moderate AS (see Supplementary data online, *Table S1*).

## RV function and pulmonary exercise haemodynamics

AS/HFpEF+ patients had a significantly decreased RV function when compared with AS/HFpEF− patients, as indicated by the tricuspid annular plane systolic excursion (15 ± 5 mm vs. 18 ± 5 mm, respectively; $P = 0.002$). They also demonstrated RV pulmonary arterial uncoupling (tricuspid

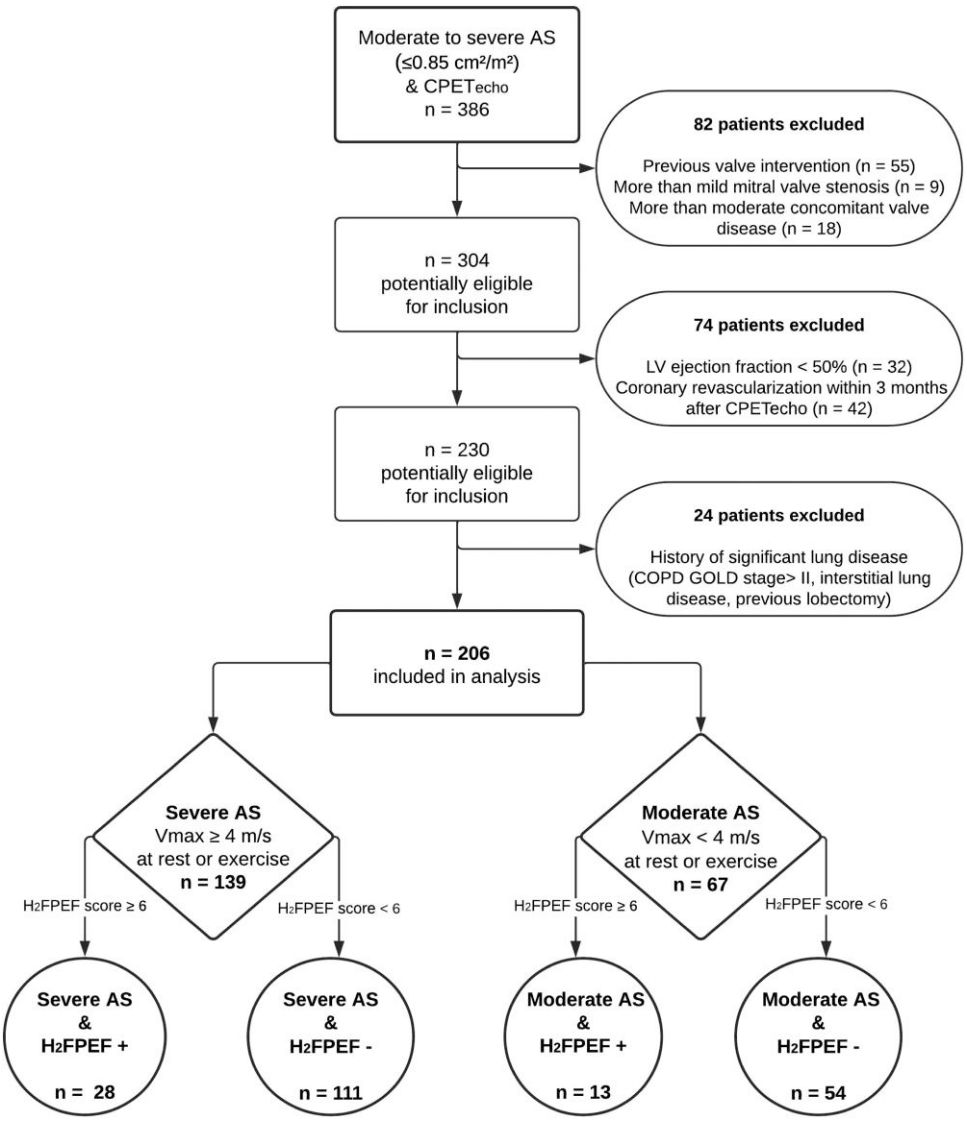



**Figure 2** Study flowchart. COPD, chronic obstructive pulmonary disease; GOLD, global initiative for obstructive lung disease.

annular plane systolic excursion over systolic pulmonary arterial pressure ratio 0.50 ± 0.22 mm/mmHg vs. 0.68 ± 0.23 mmHg, respectively; $P < 0.0001$), while this was not the case in severe vs. moderate AS (*Figure 5*; Supplementary data online, *Table S1*). Pulmonary arterial pressures at rest and submaximal exercise were increased in AS/HFpEF+ compared with AS/HFpEF−, but very alike both at rest and during exercise in severe and moderate AS (*Table 2*). CO reserve was markedly reduced in AS/HFpEF+, which was primarily driven by a lower heart rate reserve as the stroke volume index was comparable at maximal exercise between both groups. Moderate AS patients had lower stroke volume at rest than severe AS, but otherwise remarkably similar exercise haemodynamics. *Figure 6* shows the mPAP–CO relationship during exercise in the four study groups (see Supplementary data online, *Figure S4* for the sensitivity analysis according to AVA). The mPAP/CO slope was significantly increased in AS/HFpEF+ vs. AS/HFpEF− (5.4 ± 3.1 mmHg/L/min vs. 3.9 ± 2.2 mmHg/L/min, respectively; $P = 0.003$) but comparable in patients with severe vs. moderate AS (4.2 ± 2.3 mmHg/L/min vs. 4.1 ± 2.7 mmHg/L/min, respectively; $P = 0.6$; *Table 2*).

## Exercise performance

A respiratory exchange ratio ≥1 was achieved in 181 patients (88%), with 117 (57%) reaching a peak respiratory exchange ratio ≥1.1. The respiratory exchange ratio at peak exercise was alike in the HFpEF and AS severity strata. AS/HFpEF+ vs. AS/HFpEF− patients, but not patients with severe vs. moderate AS, had an impaired exercise capacity (*Table 2*). Peak $VO_2$ was significantly lower (11.5 ± 3.7 mL/min/kg vs. 15.9 ± 5.9 mL/min/kg; $P < 0.0001$), with a reduced peak oxygen pulse and increased minute ventilation to carbon dioxide production slope. In the subpopulation who had results from a computed tomography for calcium score assessment available ($n = 41$), with severe AS defined as a calcium score >2000 for men and >1200 for women, those with moderate

**Table 1** Baseline characteristics of the study population

| | Total population (*N* = 206) | HFpEF+ (*N* = 41) | HFpEF− (*N* = 165) | *P*-value HFpEF | Severe AS (*N* = 139) | Moderate AS (*N* = 67) | *P*-value AS |
|---|---|---|---|---|---|---|---|
| Age (years) | 73 ± 10 | 79 ± 8 | 72 ± 10 | N/A | 73 ± 11 | 74 ± 10 | 0.3 |
| Men, *n* (%) | 123 (60) | 20 (49) | 103 (62) | 0.2 | 82 (59) | 41 (61) | 0.9 |
| Body mass index (kg/m$^2$) | 28 ± 4 | 29 ± 5 | 27 ± 4 | N/A | 27 ± 4 | 28 ± 4 | 0.2 |
| Heart rate (bpm) | 69 ± 12 | 69 ± 13 | 69 ± 11 | 0.8 | 70 ± 12 | 68 ± 11 | 0.5 |
| Systolic BP (mmHg)[a] | 146 ± 21 | 146 ± 20 | 146 ± 22 | 0.8 | 146 ± 20 | 146 ± 24 | 0.9 |
| Diastolic BP (mmHg)[a] | 79 ± 15 | 77 ± 16 | 79 ± 15 | 0.5 | 78 ± 15 | 80 ± 15 | 0.6 |
| Bicuspid aortic valve, *n* (%) | 28 (14) | 2 (5) | 26 (16) | 0.08 | 21 (15) | 7 (10) | 0.4 |
| Hypertension, *n* (%) | 113 (55) | 34 (83) | 79 (48) | N/A | 71 (51) | 42 (63) | 0.1 |
| Diabetes, *n* (%) | 46 (22) | 13 (32) | 33 (20) | 0.1 | 37 (27) | 9 (13) | 0.03 |
| CAD, *n* (%) | 50 (24) | 10 (24) | 40 (24) | 1 | 26 (19) | 24 (36) | 0.009 |
| Atrial fibrillation, *n* (%)[b] | 56 (27) | 38 (93) | 18 (11) | N/A | 39 (28) | 17 (25) | 0.7 |
| $H_2$FPEF score | 3 (2–5) | 7 (6–7) | 3 (2–4) | N/A | 3 (2–5) | 3 (3–5) | 0.4 |
| NTproBNP (ng/L)[a] | 310 (150–830) | 620 (235–1850) | 280 (140–708) | 0.005 | 460 (160–910) | 185 (91–320) | <0.001 |
| Serum creatinine (mg/dL)[a] | 1.0 (0.8–1.2) | 1.1 (1.0–1.3) | 0.9 (0.8–1.1) | 0.002 | 1.0 (0.8–1.1) | 1.0 (0.8–1.3) | 0.8 |
| Haemoglobin (g/dL)[a] | 13.3 ± 1.8 | 12.7 ± 1.7 | 13.5 ± 1.8 | 0.02 | 13.2 ± 1.8 | 13.5 ± 1.8 | 0.4 |
| SGLT2 inhibitor use, *n* (%) | 2 (1) | 0 | 2 (1) | 1 | 2 (1) | 0 | 1 |
| Loop diuretic use, *n* (%) | 34 (17) | 13 (32) | 21 (13) | 0.008 | 21 (15) | 13 (19) | 0.4 |
| MRA use, *n* (%) | 32 (16) | 10 (24) | 22 (13) | 0.09 | 13 (9) | 19 (28) | <0.001 |
| ACE inhibitor, *n* (%) | 72 (35) | 12 (29) | 60 (36) | 0.5 | 46 (33) | 26 (39) | 0.4 |
| ARB, *n* (%) | 30 (15) | 9 (22) | 21 (13) | 0.1 | 23 (17) | 7 (10) | 0.3 |
| Beta blocker, *n* (%)r | 95 (46) | 31 (76) | 64 (39) | <0.001 | 61 (44) | 34 (51) | 0.4 |
| Amiodarone, *n* (%) | 13 (6) | 6 (15) | 7 (4) | 0.03 | 6 (4) | 7 (10) | 0.1 |
| Class I anti-arrhythmic drugs, *n* (%) | 5 (2) | 4 (10) | 1 (1) | 0.006 | 1 (1) | 4 (6) | 0.04 |

AS, aortic valve stenosis; BP, blood pressure; CAD, coronary artery disease; MRA, mineralocorticoid receptor antagonist; N/A, not available; NTproBNP, N-terminal of pro-hormone B-type natriuretic peptide; SGLT2, sodium–glucose co-transporter 2.
[a]Ten missing data for blood pressure measurements, 60 missing data for NTproBNP, 34 missing data for creatinine, 32 missing data for haemoglobin.
[b]Nine patients (4% of the overall population) had permanent AF. In those patients, A-wave amplitude and duration was quantified as 0 and left atrial strain measurements were not performed.

AS/HFpEF− had a significantly better peak VO2 (19 ± 8 mL/min/kg) vs. the other groups (severe AS/HFpEF+ 11 ± 4 mL/min/kg; severe AS/HFpEF− 13 ± 5 mL/min/kg; moderate AS/HFpEF+ 12 ± 1 mL/min/kg; $P = 0.03$).

# Discussion

The current study provides a detailed phenotypical characterization of patients with moderate to severe AS and discordant symptoms with CPETecho. LV structure, systolic and diastolic function, LA size and function, RV function, pulmonary haemodynamics, and RV–pulmonary arterial coupling were assessed. The following findings are keys: (i) in a population with moderate to severe AS and discordance between symptoms and AS lesion severity at rest, the $H_2$FPEF score identified a population with cardiac dysfunction illustrated by impaired LV diastolic function with reduced LV compliance, subtle signs of LV systolic dysfunction, more pronounced LA myopathy, and RV dysfunction with RV–pulmonary arterial uncoupling; (ii) AS severity was very similar in patients with vs. without high $H_2$FPEF score; (iii) AS/HFpEF+ patients had worse exercise haemodynamics than AS/HFpEF− with significantly higher pulmonary arterial pressures already at rest as well as during exercise and demonstrated a reduced CO reserve, resulting in a higher mPAP/CO slope; (iv) AS severity status did not influence pulmonary arterial pressures, CO reserve, or the mPAP/CO slope; and (v) HFpEF phenotype, but not AS lesion severity, was associated with impaired exercise capacity. Our highly consistent findings across multiple domains of cardiac function, haemodynamics, and exercise capacity show that HFpEF status is more important than conventionally defined AS severity using echo criteria. This calls for further study on whether incorporating the H2FPEF score might guide therapeutic decisions regarding aortic valve replacement.

The pivotal paper by Ross and Braunwald[24] in 1968 described the natural evolution of severe AS at the time and showed rapid decline around the age of 60 years together with the onset of exercise-related angina, syncope, and/or heart failure as the three cardinal symptoms of the disease. Up till today, the presence of these symptoms in AS remains an important consideration to decide on valve replacement, which only has a Class I indication for symptomatic, severe AS.[4,5] However, the clinical presentation of patients with AS has changed tremendously during the past 50 years. In 1968, rheumatic valve disease was almost the exclusive cause of AS, with a disease onset in relatively healthy individuals. Fast forward until today and degenerative calcified valve disease has overtaken as the predominant cause of AS in North

**Table 2** Cardiopulmonary exercise test results and exercise haemodynamics

| | Total population (*N* = 206) | HFpEF+ (*N* = 41) | HFpEF− (*n* = 165) | *P*-value HFpEF | Severe AS (*N* = 139) | Moderate AS (*N* = 67) | *P*-value AS |
|---|---|---|---|---|---|---|---|
| Aortic valve | | | | | | | |
| Vmax (m/s) | | | | | | | |
| Rest | 3.8 ± 0.8 | 3.8 ± 0.7 | 3.7 ± 0.8 | 0.6 | 4.1 ± 0.6 | 2.9 ± 0.4 | N/A |
| Submaximal exercise | 4.1 ± 0.7 | 4.1 ± 0.6 | 4.1 ± 0.8 | 0.7 | 4.4 ± 0.6 | 3.3 ± 0.4 | N/A |
| Peak exercise | 4.3 ± 0.7 | 4.3 ± 0.6 | 4.4 ± 0.7 | 0.7 | 4.7 ± 0.5 | 3.6 ± 0.3 | N/A |
| Vmax ≥4 m/s, *n* (%) | | | | | | | |
| Rest | 85 (41) | 20 (49) | 65 (39) | 0.3 | 85 (61) | 0 | N/A |
| Peak exercise | 139 (67) | 28 (68) | 111 (67) | 1 | 139 (100) | 0 | N/A |
| Mean gradient (mmHg) | | | | | | | |
| Rest | 38 ± 16 | 39 ± 15 | 37 ± 17 | 0.6 | 45 ± 14 | 22 ± 6 | N/A |
| Submaximal exercise | 45 ± 17 | 45 ± 15 | 45 ± 18 | 0.9 | 53 ± 15 | 28 ± 7 | N/A |
| Peak exercise | 50 ± 18 | 49 ± 17 | 51 ± 19 | 0.6 | 59 ± 15 | 32 ± 7 | N/A |
| Δ Mean gradient with exercise (mmHg) | 13 ± 9 | 10 ± 7 | 14 ± 10 | 0.03 | 15 ± 11 | 10 ± 5 | N/A |
| AVA ($cm^2$) | | | | | | | |
| Rest | 0.9 ± 0.3 | 0.8 ± 0.3 | 0.9 ± 0.3 | 0.1 | 0.8 ± 0.2 | 1.1 ± 0.2 | N/A |
| Submaximal exercise | 1.0 ± 0.3 | 0.9 ± 0.3 | 1.0 ± 0.3 | 0.03 | 0.9 ± 0.3 | 1.2 ± 0.2 | N/A |
| Peak exercise | 1.0 ± 0.3 | 0.9 ± 0.3 | 1.1 ± 0.3 | 0.01 | 1.0 ± 0.3 | 1.2 ± 0.3 | N/A |
| Exercise performance | | | | | | | |
| Peak RER | 1.1 ± 0.1 | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.6 | 1.1 ± 0.1 | 1.1 ± 0.1 | 0.5 |
| Peak $VO_2$ (mL/min/kg) | 15.0 ± 5.8 | 11.5 ± 3.7 | 15.9 ± 5.9 | <0.001 | 15.2 ± 5.9 | 14.7 ± 5.5 | 0.6 |
| Percent predicted METs | 71 ± 21 | 63 ± 15 | 73 ± 21 | 0.002 | 71 ± 20 | 71 ± 21 | 0.9 |
| ≥100%, *n* (%) | 22 (11) | 1 (2) | 21 (13) | 0.09 | 13 (9) | 9 (13) | 0.5 |
| <60%, *n* (%) | 62 (30) | 16 (39) | 46 (28) | 0.2 | 40 (29) | 22 (33) | 0.5 |
| Δ$VO_2$/power (mL/min/W) | 11 (10–14) | 12 (10–14) | 11 (10–13) | 0.5 | 11 (10–14) | 12 (11–13) | 0.3 |
| $V_E/VCO_2$ slope | 31 ± 6 | 34 ± 6 | 30 ± 6 | <0.001 | 31 ± 6 | 32 ± 7 | 0.2 |
| Peak $VO_2$/HR (mL/min/beat) | 10.2 ± 3.4 | 9.2 ± 3.8 | 10.4 ± 3.2 | 0.03 | 10.2 ± 3.4 | 10.1 ± 3.3 | 0.9 |
| Exercise haemodynamics | | | | | | | |
| HR (bpm) | | | | | | | |
| Rest | 69 ± 12 | 69 ± 13 | 69 ± 11 | 0.8 | 70 ± 12 | 68 ± 11 | 0.5 |
| Submaximal exercise | 93 ± 16 | 88 ± 16 | 94 ± 15 | 0.02 | 94 ± 16 | 91 ± 14 | 0.1 |
| Peak exercise | 115 ± 22 | 104 ± 19 | 118 ± 22 | <0.001 | 116 ± 22 | 115 ± 21 | 0.8 |
| Stroke volume index ($mL/m^2$) | | | | | | | |
| Rest | 38 ± 9 | 38 ± 10 | 39 ± 9 | 0.7 | 39 ± 9 | 36 ± 9 | 0.03 |
| Submaximal exercise | 44 ± 9 | 42 ± 8 | 45 ± 9 | 0.1 | 45 ± 10 | 43 ± 8 | 0.2 |
| Peak exercise | 43 ± 10 | 42 ± 8 | 44 ± 10 | 0.2 | 44 ± 11 | 43 ± 8 | 0.5 |
| Cardiac index ($mL/m^2$) | | | | | | | |
| Rest | 2.6 ± 0.7 | 2.6 ± 0.7 | 2.6 ± 0.7 | 0.5 | 2.7 ± 0.7 | 2.5 ± 0.6 | 0.008 |
| Submaximal exercise | 4.1 ± 1.0 | 3.7 ± 0.7 | 4.2 ± 1.0 | <0.001 | 4.2 ± 1.0 | 3.9 ± 0.9 | 0.06 |
| Peak exercise | 5.0 ± 1.2 | 4.3 ± 1.0 | 5.2 ± 1.2 | <0.001 | 5.1 ± 1.3 | 4.9 ± 1.1 | 0.3 |
| sPAP (mmHg) | | | | | | | |
| Rest | 28 ± 6 | 32 ± 10 | 27 ± 4 | 0.001 | 28 ± 7 | 27 ± 6 | 0.7 |
| Submaximal exercise | 52 ± 10 | 58 ± 12 | 50 ± 9 | <0.001 | 52 ± 10 | 52 ± 10 | 0.8 |
| Peak exercise | 61 ± 10 | 64 ± 12 | 61 ± 10 | 0.08 | 62 ± 10 | 60 ± 11 | 0.3 |
| mPAP/CO slope | 4.2 ± 2.5 | 5.4 ± 3.1 | 3.9 ± 2.2 | 0.003 | 4.3 ± 2.3 | 4.1 ± 2.7 | 0.6 |

AS, aortic valve stenosis; CO, cardiac output; HR, heart rate; METs, metabolic equivalents; mPAP, mean pulmonary arterial pressure; N/A, not available; RER, respiratory exchange ratio; sPAP, systolic pulmonary arterial pressure; $V_E/VCO_2$, minute ventilation to carbon dioxide production; $VO_2$, oxygen uptake; Vmax, peak aortic transvalvular velocity.

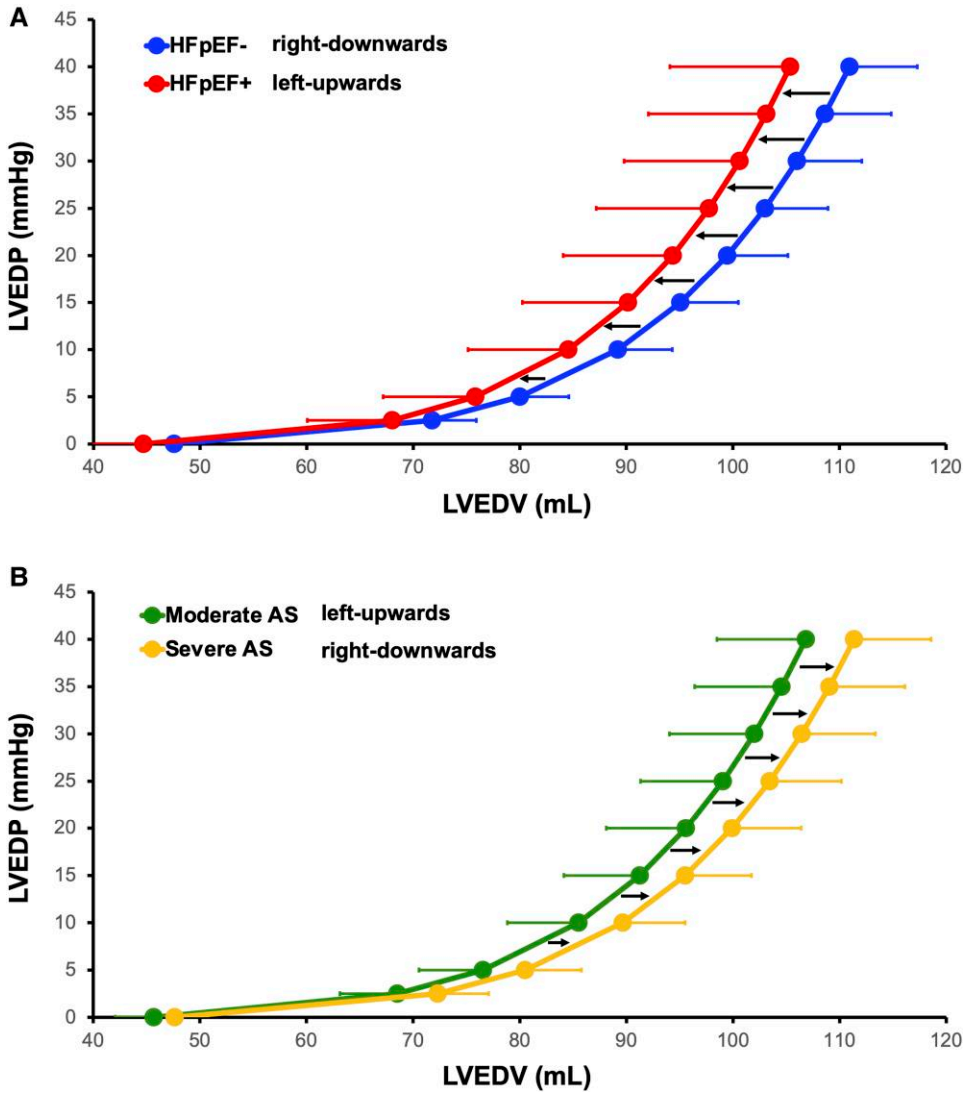



**Figure 3** Left ventricular end-diastolic pressure–volume relationship according to (*A*) the likelihood of underlying heart failure with preserved ejection fraction by the $H_2$FPEF score (≥6 vs. <6) and (*B*) the severity of aortic valve stenosis (peak aortic jet velocity ≥4 m/s vs. <4 m/s). Bars indicate 95% confidence intervals. LVEDP, left ventricular end-diastolic pressure; LVEDV, left ventricular end-diastolic volume.

America and Western Europe, with patients typically presenting at an older age with more frequent co-morbid conditions and more severe frailty.[25] This observation has two important consequences. First, while AS was formerly a simple disease whereby cardiac dysfunction could almost exclusively be attributed to a single valve lesion, concomitant intrinsic myocardial disease nowadays has become more frequent, which complicates the haemodynamic interpretation and assessment of cardiac damage that can be attributed to the valve disease. Secondly, the presence of co-morbid conditions, frailty, and lower activity levels in patients with AS has made the onset of symptoms more difficult to interpret. Indeed, many of the risk factors for AS are also concomitant risk factors for the commonest cause of heart failure: inflammatory and comorbidity-driven HFpEF. Another major evolution has been the development of less invasive percutaneous options for aortic valve replacement that have significantly reduced the procedural risks of a definite treatment for AS. Consequently, there is a general tendency to intervene earlier in AS, potentially even before emergent cardinal symptoms.[26–28] Randomized clinical trials such as the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement trial (NCT04889872) are investigating this strategy. These trials will answer the question whether percutaneous valve replacement improves hard clinical outcomes in symptomatic patients with moderate AS. The current study further supports a disconnect among symptoms, objective exercise intolerance, adverse haemodynamics, and valve lesion severity in a contemporary population with moderate to severe AS. Importantly, the present data suggest a new approach to AS, using evaluation for evidence of clinical heart failure with the $H_2$FPEF score as a potentially important means to guide clinical decision-making regarding timing of aortic valve replacement, in addition to assessment of AS severity. This requires testing in prospective randomized trials.

An important finding of the current study is that patients with AS, who present with a HFpEF-like signature, have a clearly impaired objective exercise capacity, while the AS severity seems to be less of an

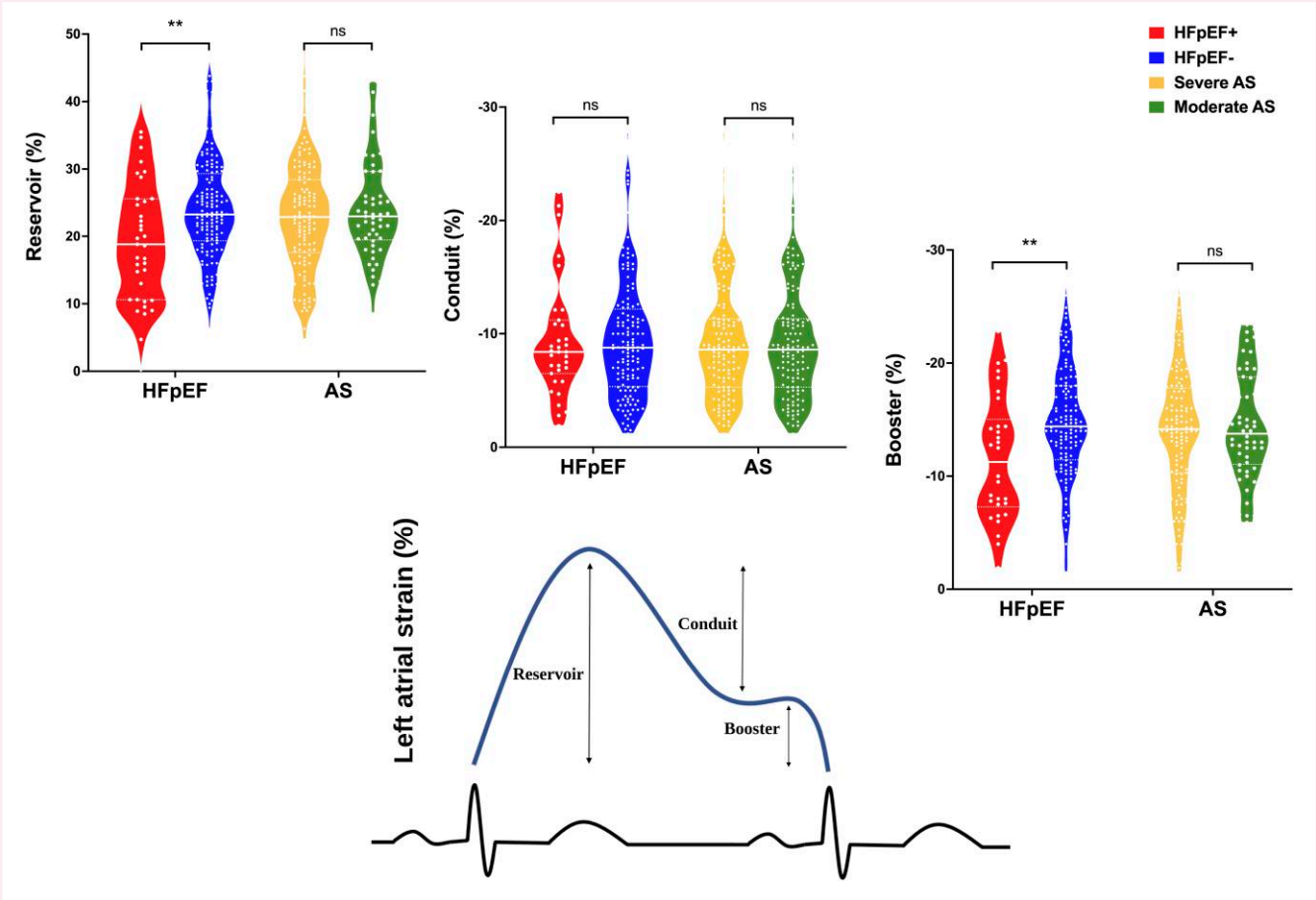



**Figure 4** Left atrial strain in the reservoir, conduit, and booster pump phase according to the likelihood of underlying heart failure with preserved ejection fraction by the $H_2$FPEF score (≥6 in red vs. <6 in green).

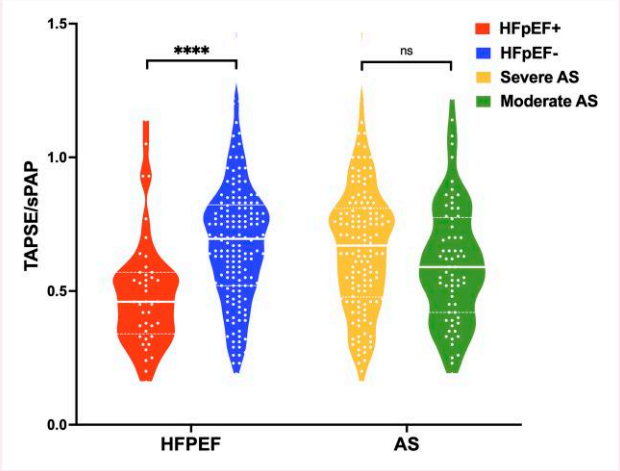



**Figure 5** Right ventricular pulmonary arterial uncoupling as indicated by the tricuspid annular plane systolic excursion (TAPSE) over right ventricular systolic pressure (sPAP) ratio according to the likelihood of underlying heart failure with preserved ejection fraction by the $H_2$FPEF score (≥6 in red vs. <6 in green) and the severity of aortic valve stenosis (peak aortic jet velocity ≥4 m/s in yellow vs. <4 m/s in blue).

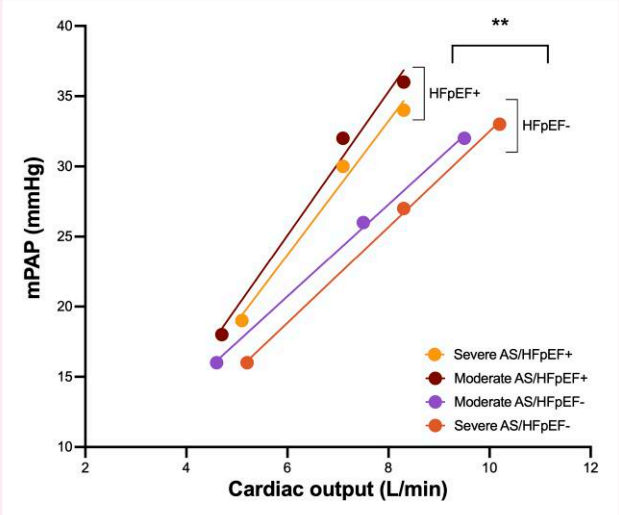



**Figure 6** Mean pulmonary arterial pressure (mPAP)-cardiac output relationship during exercise according to the likelihood of underlying heart failure with preserved ejection fraction by the $H_2$FPEF score (≥6 vs. <6) and severity of aortic valve stenosis (peak aortic jet velocity ≥4 m/s vs. <4 m/s).

influential factor. Therefore, especially when interpreting less specific symptoms in AS like dyspnoea or fatigue, one needs to realize that they poorly reflect the intrinsic severity of the valve disease but are instead closely related to cardiac damage and dysfunction. The extent of such cardiac damage and dysfunction, as well as their change over time, bears important prognostic implications after aortic valve replacement.[2,9] In this study, the $H_2$FPEF score (as a simple bedside tool) performed well to identify a group of patients with a HFpEF-like signature within a population with moderate to severe AS. Indeed, patients with a high $H_2$FPEF score had characteristic HFpEF features such as LV hypertrophy, impaired diastolic function with a stiffer ventricle, more pronounced LA myopathy, and more advanced pulmonary vascular and RV dysfunction. Although the $H_2$FPEF score has been originally developed and validated in a completely different population of patients with unexplained dyspnoea, current findings suggest that a broader application is possible.[10] Indeed, even among patients without heart failure or valve disease, higher $H_2$FPEF score is associated with cardiac, haemodynamic, and exertional abnormalities indicating pre-clinical cardiac insufficiency.[14] It has already been demonstrated that the $H_2$FPEF score is highly prognostic in both patients with HFpEF and those undergoing transcatheter aortic valve implantation.[11–13] This study further advances this growing literature, showing through detailed cardiac structural and functional phenotyping that a higher $H_2$FPEF score identifies patients with more severe cardiac impairment and poorer exercise haemodynamics and objective functional capacity.

While a high $H_2$FPEF score was associated with subtle signs of LV systolic dysfunction, RV function was markedly reduced with signs of RV–pulmonary arterial uncoupling. RV rather than LV function is more intrinsically linked with exercise capacity in heart failure, representing a powerful prognosticator as well.[1,3,23,29] The current results show a higher mPAP/CO slope with exercise in patients with a high $H_2$FPEF score, which was predominantly driven by an impaired CO reserve during exercise. This suggests that RV dysfunction plays an important role in the objective exercise intolerance of patients with moderate to severe AS, and interventions should probably be employed before its occurrence. Recent data have shown that aortic valve replacement acutely improves RV function and RV–pulmonary arterial coupling, further emphasizing the importance for potentially targeting patients identified in this manner.[30]

## Clinical implications

The current study might be an incentive to further study the role of CPETecho for clinical decision-making in patients with moderate to severe AS without unequivocal high-risk symptoms such as exertional syncope or typical angina. CPET offers objective criteria for exercise capacity. As poor correspondence between objective functional status and valve lesion severity was demonstrated, reliance on subjective symptoms like dyspnoea or fatigue likely contributes little to determine whether the AS is severe and neither would be expected to predict symptomatic improvement after intervention, questioning the strong reliance on non-specific symptoms for AS treatment decisions. Furthermore, it is important to realize that a low stroke volume index $<35$ mL/m$^2$ at rest is present in almost 40% of the general population, complicating the haemodynamic assessment of AS.[31] When severity of AS was based on AVA rather than Vmax, stroke volume and CO were lower in patients with severe AS, which was associated with impaired exercise capacity. Our current diagnostic approach towards paradoxical low-flow low-gradient severe AS is limited to an integration of the valvular calcium score, echocardiography findings, the clinical presentation, and sometimes invasive haemodynamic measurements.[4,5] CPETecho may offer insightful information in such cases on contractile reserve, evolution of gradients and valve area during exercise, exercise haemodynamics, and objective exercise capacity. Further prospective studies are needed to determine its exact diagnostic and prognostic value.

## Study limitations

First, this is a single-centre study in a tertiary valve referral center, which may limit external validity due to referral bias. Secondly, because AS severity strata were based on Vmax for the main analyses of this study, patients with paradoxical low-flow, low-gradient, severe AS were more likely to be classified as moderate AS. However, the proportion of such patients was evenly distributed among HFpEF strata. Moreover, a sensitivity analysis using AVA to determine AS severity showed consistent results. Thirdly, while the $H_2$FPEF score was used to identify patients with a HFpEF signature in our population, the possibility that the presence of AS influenced some of the factors in the score (e.g. high filling pressures) cannot be excluded. Therefore, whether HFpEF was caused by structural cardiac damage due to the presence of AS vs. the consequence of an intrinsic myocardial disease process cannot be determined. However, it is reassuring to observe that every individual factor of the $H_2$FPEF score was similarly distributed among the moderate vs. severe AS groups. Fourthly, 15% of patients with presumed asymptomatic severe AS were treated with loop diuretics. It is possible that without these drugs they would have been symptomatic, thus directly qualifying for valve replacement rather than exercise testing according to current guidelines. Fifthly, between 10% and 30% of patients in real-world clinical practice are not able to perform exercise stress testing for different reasons. Finally, exercise haemodynamics were assessed non-invasively with echocardiography rather than though invasive measurements.

# Conclusions

In this study, it was shown that a high $H_2$FPEF score in patients with moderate to severe AS is associated more pronounced with cardiac dysfunction, adverse haemodynamics and impaired exercise capacity (Graphical Abstract). Moreover, HFpEF signature by the $H_2$FPEF score was more discriminative than AS severity defined by conventional echocardiography criteria.

# Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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**Conflict of interest:** None declared.

## Data availability

Raw data are available upon reasonable request to the corresponding author.

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