Shedding Light on Latent Pulmonary Vascular Disease in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

BACKGROUND Among patients with heart failure with preserved ejection fraction (HFpEF), a distinct hemodynamic phenotype has been recently described, ie, latent pulmonary vascular disease (HFpEF-latentPVD), defined by exercise pulmonary vascular resistance (PVR) >1.74 WU.

OBJECTIVES This study aims to explore the pathophysiological significance of HFpEF-latentPVD.

METHODS The authors analyzed a cohort of patients who had undergone supine exercise right heart catheterization with cardiac output (CO) measured by direct Fick method, between 2016 and 2021. HFpEF-latentPVD patients were compared with HFpEF control patients.

RESULTS Out of 86 HFpEF patients, 21% qualified as having HFpEF-latentPVD, 78% of whom had PVR >2 WU at rest. Patients with HFpEF-latentPVD were older, with a higher pretest probability of HFpEF, and more frequently experienced atrial fibrillation and at least moderate tricuspid regurgitation ($P < 0.05$). PVR trajectories differed between HFpEF-latentPVD patients and HFpEF control patients ($P_{interaction} = 0.008$), slightly increasing in the former and reducing in the latter. HFpEF-latentPVD patients displayed more frequent hemodynamically significant tricuspid regurgitation during exercise ($P = 0.002$) and had more impaired CO and stroke volume reserve ($P < 0.05$). Exercise PVR was correlated with mixed venous O_2 tension ($R^2 = 0.33$) and stroke volume ($R^2 = 0.31$) in HFpEF-latentPVD patients. The HFpEF-latentPVD patients had had higher dead space ventilation during exercise and higher $PaCO_2$ ($P < 0.05$), which correlated with resting PVR ($R^2 = 0.21$). Event-free survival was reduced in HFpEF-latentPVD patients ($P < 0.05$).

CONCLUSIONS The results suggest that when CO is measured by direct Fick, few HFpEF patients have isolated latent PVD (ie, normal PVR at rest, becoming abnormal during exercise). HFpEF-latentPVD patients present with CO limitation to exercise, associated with dynamic tricuspid regurgitation, altered ventilatory control, and pulmonary vascular hyperreactivity, portending a poor prognosis. (J Am Coll Cardiol HF 2023;11:1427–1438) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CO = cardiac output

HFpEF = heart failure with preserved ejection fraction

PaCO₂ = arterial partial pressure for carbon dioxide

PAWP = pulmonary artery wedge pressure

PVD = pulmonary vascular disease

PVR = pulmonary vascular resistance

RAP = right atrial pressure

VO₂ = oxygen consumption

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent condition, associated with high left-sided cardiac filling pressure at rest and/or during exercise.[1] Backward transmission of high left cardiac filling pressure to the pulmonary circulation, leading to postcapillary pulmonary hypertension,[2] may promote pulmonary vascular remodeling over time, with increased pulmonary vascular resistance (PVR) and combined postcapillary and precapillary pulmonary hypertension in predisposed individuals.[3,4] The linear association between higher PVR and adverse clinical outcomes[5] recently led the European Society of Cardiology to lower the threshold to identify the precapillary component of pulmonary hypertension (PVR >2 WU).[2] Additionally, a post hoc analysis of the REDUCE LAP-HF II (A Study to Evaluate the Corvia Medical, Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) trial[6] highlighted that exercise PVR >1.74 WU may identify a worse clinical and hemodynamic phenotype of HFpEF patients, called HFpEF with latent pulmonary vascular disease (PVD).[7] Individuals with HFpEF-latentPVD may respond poorly to the creation of an interatrial septal defect, and they may not be correctly identified when undergoing only a resting hemodynamic evaluation.[7]

In consequence, there is a need to better understand the pathophysiology of patients with HFpEF and an overt or latent precapillary component, which may help the design of ad hoc treatment for this subgroup of patients at higher risk of adverse events and without any available treatment strategy.[2]

The aim of our study was to explore the clinical characteristics of HFpEF patients with latent PVD, as well as hemodynamic and cardiorespiratory adaptation to exercise of this peculiar phenotype. To do so, we performed a single-center, retrospective data analysis of serial patients with known or newly diagnosed HFpEF in our catheterization laboratory.

METHODS

This study was approved by the Ethics Committee of the Istituto Auxologico Italiano (protocol n 2022_09_27_01 approved on September 27, 2022). Signature of informed consent for this data analysis was waived because of the retrospective nature of the study, but at the time of right heart catheterization all patients had signed written informed consent to allow the use of their clinical data for research purposes.

We analyzed the consecutive cohort of patients who underwent an elective, clinically indicated cardiac catheterization at rest and during exercise at Istituto Auxologico Italiano between January 2016 and December 2021.

First, we identified patients who responded to the hemodynamic diagnosis of HFpEF, ie, those with compatible signs and symptoms as well as a pulmonary artery wedge pressure (PAWP) at rest >15 mm Hg, or a PAWP at peak exercise ≥25 mm Hg, or a PAWP/cardiac output (CO) slope >2 mm Hg/L/min.[8,9] Then, we subdivided this cohort of patients based on PVR at peak exercise: >1.74 WU (HFpEF-latentPVD) or ≤1.74 WU (HFpEF control patients).[7]

We excluded patients with left ventricular ejection fraction <50%, secondary forms of HFpEF (cardiomyopathy, infiltrative diseases, pericardial constriction), more than mild left-sided valvular heart disease, congenital heart disease; clinical and hemodynamic diagnosis of pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or chronic thromboembolic pulmonary disease, pulmonary hypertension caused by lung disease and/or hypoxia; severe comorbidities (chronic obstructive pulmonary disease with GOLD classification ≥3, severe restrictive lung disease, severe obesity with body mass index >40 kg/m², severe anemia with hemoglobin ≤9 g/dL, end-stage chronic kidney disease), and normal hemodynamics at rest and during exercise.

Clinical and echocardiographic data, obtained at the time of a structured assessment preceding the indication for cardiac catheterization, were analyzed to calculate both the pretest probability of HFpEF based on the H₂FPEF (heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure) score[10] and the HFA-PEFF (Heart Failure Association-Pretest assessment, Echocardiography and Natriuretic Peptide) score.[11] These data were generally collected during the 15 days before cardiac catheterization, provided that no change in clinical status, symptoms, or treatment had occurred between the noninvasive assessment and cardiac catheterization. The H₂FPEF score[10] is a continuous score with higher values associated with higher probability of HFpEF. For practical reasons, we considered HFpEF "likely" in those patients with a H₂FPEF score >4 (probability >70%), HFpEF "possible" in those with a H₂FPEF score 2 to 4 (probability 40%-70%), and HFpEF "unlikely" in

TABLE 1 Dichotomization of Hemodynamic Profiles at Rest and During Exercise

	Rest		Peak	
	No	**Yes**	**No**	**Yes**
Pulmonary hypertension	mPAP ≤20 mm Hg	mPAP >20 mm Hg	mPAP/CO slope ≤3	mPAP/CO slope >3
LA hypertension	PAWP ≤15 mm Hg	PAWP >15 mm Hg	PAWP <25 mm Hg and/or PAWP/CO slope ≤2	PAWP ≥25 mm Hg and/or PAWP/CO slope >2
LA dysfunction	PAWP V-wave amplitude ≤5 mm Hg	PAWP V-wave amplitude >5 mm Hg	PAWP V-wave amplitude ≤5 mm Hg	PAWP V-wave amplitude >5 mm Hg
Precapillary component	PVR <2 WU	PVR >2 WU	PVR ≤1.74 WU	PVR >1.74 WU
Tricuspid regurgitation	RAP V-wave − RAP nadir ≤8 mm Hg	RAP V-wave − RAP nadir >8 mm Hg	RAP V-wave − RAP nadir ≤8 mm Hg	RAP V-wave − RAP nadir >8 mm Hg
Low CO	CI ≥2.2 L/min/m²	CI <2.2 L/min/m²	CO ≥80% of predicted	CO <80% of predicted
Low CO increase			CO/VO₂ slope ≥4.7	CO/VO₂ slope <4.7

CI = cardiac index; CO = cardiac output; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; VO₂ = oxygen consumption.

those with a H_2FPEF score <2 (probability <40%). The HFA-PEFF score[11] categorizes patients as HFpEF "likely" (score >4), HFpEF "possible" (score 2-4), and HFpEF "unlikely" (score <2).

ECHOCARDIOGRAPHY. Echocardiography was performed according to current recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography by experienced cardiologists,[12] using a Vivid E9/E95 scanners (GE Vingmed). Left ventricular and left atrial volumes were measured by biplane disk summation algorithm on dedicated 4-chamber and 2-chamber apical views, care being taken to avoid chamber foreshortening. Echocardiographic evaluation of valvular regurgitation was based on an integrative approach considering multiple qualitative and quantitative parameters.[13]

RIGHT HEART CATHETERIZATION AND CARDIOPULMONARY EXERCISE TEST. Patients were studied while receiving optimized medical therapy and in a euvolemic non-fasting state, without sedation, and in a supine position. They wore a nonrebreathing Hans-Rudolph mask connected to the V-MAX metabolic cart (Vmax SensorMedics 2200) to directly measure gas exchange data and ventilation.[8] A 7-F fluid-filled Swan-Ganz catheter was placed in the pulmonary artery through the right internal jugular vein under fluoroscopic guidance. Proper pulmonary artery wedge positioning was confirmed by the appearance of a typical PAWP trace and by an O_2 saturation >94% sampled at the tip of the catheter. The right radial artery was cannulated with the Seldinger technique. Hemodynamic measurements were performed at rest, after 1 minute of passive leg raise (feet on the pedals), and during the last minute of each step of a symptom-limited, maximal exercise test.[8] Blood was sampled

from the tip of the Swan-Ganz catheter and from the radial artery for blood gas analysis. The subjects were encouraged to exercise up to their maximal volitional effort.

Key ergospirometric measurements included standard breath-by-breath cardiorespiratory and breathing pattern parameters. Peak O_2 consumption (VO₂) was measured as the highest 30-second value obtained at the end of the effort. Minute ventilation was normalized for CO_2 production. Dead space ventilation was calculated based on standard formula.[14]

Pulmonary artery pressure, PAWP, and right atrial pressure (RAP) were measured at end-expiration over several cardiac and respiratory cycles.[8] In addition to end-expiratory mean PAWP and RAP, the diastolic and systolic components of each atrial pressure were evaluated, including the following:

- End-diastolic PAWP and RAP: mid-A for in patients in sinus rhythm and mid-C (when visible) or pre-V for patients in atrial fibrillation
- PAWP V amplitude: the difference between V-wave and mean PAWP[8]
- Systolic increase in RAP: the difference between right atrium V-wave and RAP nadir, reflecting the severity of tricuspid regurgitation[15]

Hemodynamic data reflect the agreement of 2 readers who visually reviewed all pressure traces. CO was calculated by the direct Fick method, solving the O_2 consumption (VO₂) equation as follows: $CO = VO_2/$ arteriovenous O_2 difference. Furthermore, to evaluate the relative contribution of the elements of the Fick equation to exercise capacity, we plotted CO as a function of peripheral O_2 extraction, ie, arteriovenous O_2 difference/arterial O_2 content.[16]

TABLE 2 Clinical Characteristics of the Study Groups

	HFpEF Control Patients (n = 68)	HFpEF-LatentPVD Patients (n = 18)	P Value
Demographic and anthropometrics			
Age, y	72 (67-78)	77 (71-81)	0.025
Female	46 (68)	13 (72)	0.710
BMI, kg/m²	27.0 ± 5.6	26.3 ± 4.6	0.607
Vital signs			
SBP, mm Hg	132 ± 16	130 ± 17	0.602
DBP, mm Hg	75 ± 11	74 ± 12	0.761
HR, mm Hg	70 ± 11	69 ± 10	0.807
Rhythm			0.004
Sinus rhythm	48 (71)	8 (44)	
Paroxysmal AF	12 (18)	1 (6)	
Persistent AF	6 (9)	6 (33)	
Permanent AF	2 (3)	3 (17)	
Comorbidities			
Obesity	20 (29)	2 (11)	0.139
Arterial hypertension	50 (74)	16 (89)	0.221
Diabetes mellitus/impaired glucose tolerance	7 (10)	7 (39)	0.003
Coronary artery disease	9 (13)	5 (28)	0.158
History of pulmonary embolism	5 (7)	2 (11)	0.633
Smoking history	27 (40)	5 (28)	0.420
COPD (only GOLD I-II)	18 (26)	4 (22)	1.000
Obstructive sleep apnea	15 (22)	4 (22)	1.000
Implanted pace-maker	8 (12)	4 (22)	0.266
AF ablation	6 (9)	3 (17)	0.388
Thoracic radiotherapy	9 (13)	2 (11)	1.000
Blood test results			
Hemoglobin, g/dL	13.3 ± 1.6	12.6 ± 1.7	0.103
Creatinine, mg/dL	0.93 (0.81-1.02)	1.07 (0.71-1.29)	0.512
BNP, ng/L	99 (55-210), n = 49/68	88 (42-414), n = 12/18	0.684
proBNP, ng/L	193 (55-408), n= 41/68	673 (304-881), n = 13/18	0.013
Echocardiography			
LVEF, %	64 (62-66)	61 (54-65)	0.007
LVEDVI, mL/m²	47 (41-64)	46 (42-59)	0.691
IVS thickness, mm	10.3 ± 1.4	10.8 ± 1.0	0.167
PW thickness, mm	9.3 ± 1.2	9.8 ± 1.1	0.176
LAVI, mL/m²	34 (26-49)	43 (30-51)	0.166
E/E′	9.2 (8.1-12.0)	11.5 (7.7-14.9)	0.236
Estimated PASP, mm Hg	33 (28-45)	40 (35-53)	0.003
Moderate or > moderate TR	19 (28)	11 (61)	0.009
Moderate MR	5 (7)	4 (22)	0.087
Probability of HFpEF			
H₂FPEF score	3.9 ± 2.0	5.1 ± 2.0	0.022
H₂FPEF score >4	36 (53)	13 (72)	0.142
HFA-PEFF score	3.3 ± 2.0	4.8 ± 1.3	0.004
HFA-PEFF score >4	22 (32)	10 (56)	0.070

Values are median (IQR), n (%), or mean ± SD.

AF = atrial fibrillation; BMI = body mass index; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; GOLD = global initiative for obstructive lung disease; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; IVS = interventricular septum; LAVI = left atrial volume index; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; PW = posterior wall; PASP = pulmonary artery systolic pressure; SBP = systolic blood pressure; TR = tricuspid regurgitation.

Pivotal hemodynamic variables were also dichotomized (normal vs pathologic) both at rest and during exercise, based on previously described cutoff values, as shown in Table 1. This served to define, during each stage of the test (rest and exercise), the following predefined hemodynamic phenotypes: pulmonary hypertension,[2] left atrial hypertension,[8] left atrial dysfunction as determined by the presence of tall PAWP V waves (V-wave amplitude >5 mm Hg) in the absence of significant mitral regurgitation,[8] precapillary pulmonary vascular component,[2,7] severe tricuspid regurgitation,[15] and low CO or low CO increase.[17]

FOLLOW-UP. Relevant clinical events occurring during the follow-up (hospitalization for heart failure, access to the emergency department >12 hours and/or need of intravenous diuretics, death) were captured through a review of electronic medical records by an investigator blinded to the hemodynamic data.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD or median (IQR) if the data did not follow a normal distribution. The categorical variables are shown as absolute frequencies and proportions. For baseline characteristics, comparisons between HFpEF-latentPVD patients and HFpEF control patients were performed by unpaired Student's *t*-test (or Wilcoxon rank sum test in case of nonnormal distribution) for continuous variables and by chi-square test (or Fisher test) for categorical variables. For each hemodynamic variable measured during exercise, a linear mixed-effect model for repeated measures was fitted, considering an unstructured variance-covariance matrix to take into account the correlation among measurements on the same subjects. The included covariates in each model were group (HFpEF-latentPVD patients and HFpEF control patients), step (rest and peak exercise), and their interaction. The statistical significance of interaction term suggested a different trend of the hemodynamic variables between groups. Moreover, we tested the least square means differences among groups at each step by means of unpaired Student's *t*-test.

Kaplan-Meier curves were used to estimate the event-free survival rates in HFpEF-latentPVD patients and HFpEF control patients, and, in an exploratory analysis, the differences between groups were evaluated through the log-rank test.

All analyses were performed with SAS version 9.4 software (SAS Institute). Statistical significance was set at the 0.05 level. All *P* values were 2-sided.

TABLE 3 Resting and Exercise Hemodynamics in the 2 Study Groups

	Rest			Exercise		
	HFpEF Control Patients	HFpEF-LatentPVD Patients	*P* Value	HFpEF Control Patients	HFpEF-LatentPVD Patients	*P* Value
Hemodynamics						
Mean PAP, mm Hg	20 ± 1	26 ± 2	0.006	41 ± 1	47 ± 2	0.021
End-diastolic PAWP, mm Hg	8 ± 1	8 ± 1	0.797	20 ± 1	23 ± 2	0.292
Mean PAWP, mm Hg	14 ± 1	16 ± 2	0.308	34 ± 1	30 ± 2	0.145
PAWP V amplitude, mm Hg	4 ± 1	5 ± 1	0.171	9 ± 1	9 ± 2	0.933
Mean RAP, mm Hg	7 ± 1	6 ± 1	0.603	17 ± 1	18 ± 2	0.788
End-diastolic RAP, mm Hg	7 ± 1	6 ± 1	0.521	17 ± 1	16 ± 2	0.818
RAP systolic increase, mm Hg	2 ± 1	3 ± 1	0.487	6 ± 1	10 ± 2	0.009
PVR, WU	1.3 ± 0.1	2.4 ± 0.2	<0.001	0.8 ± 0.1	2.6 ± 0.1	<0.001
HR, beats/min	69 ± 2	71 ± 3	0.520	111 ± 3	105 ± 5	0.347
CO, L/min	4.7 ± 0.2	4.3 ± 0.4	0.246	9.7 ± 0.3	6.9 ± 0.6	<0.001
SV, mL	69 ± 3	62 ± 5	0.258	88 ± 3	68 ± 5	0.001
Ventilation and gas exchange						
VO_2, mL	195 ± 15	209 ± 8	0.424	1,097 ± 42	828 ± 80	0.004
PvO_2, mm Hg	40 ± 1	40 ± 1	0.831	25 ± 1	22 ± 1	0.010
SvO_2, %	72 ± 1	69 ± 1	0.073	38 ± 1	30 ± 2	<0.001
$CavO_2$, mL/dL	4.5 ± 0.1	4.6 ± 0.2	0.694	11.4 ± 0.3	12.1 ± 0.5	0.244
$CavO_2/CaO_2$	0.25 ± 0.01	0.28 ± 0.01	0.036	0.60 ± 0.01	0.68 ± 0.02	<0.001
Hb, g/dL	13.4 ± 0.2	12.4 ± 0.4	0.021	14.2 ± 0.2	13.3 ± 0.4	0.076
VE, L/min	8.2 ± 0.4	8.2 ± 0.7	0.971	38.3 ± 1.6	30.8 ± 3.0	0.031
$VECO_2$	55.0 ± 1.9	55.7 ± 3.6	0.866	35.7 ± 0.7	36.2 ± 1.3	0.758
V_D/V_T	0.50 ± 0.06	0.63 ± 0.11	0.328	0.35 ± 0.01	0.40 ± 0.02	0.030
$PaCO_2$, mm Hg	39 ± 1	43 ± 1	0.002	39 ± 1	41 ± 1	0.026

Values are mean ± SD. Hb = hemoglobin; $PaCO_2$ = arterial partial pressure for carbon dioxide; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PvO_2 = mixed venous oxygen pressure; PVR = pulmonary vascular resistance; SV = stroke volume; SvO_2 = mixed venous oxygen saturation; V_D/V_T = dead space ventilation; VE = minute ventilation; $VECO_2$ = minute ventilation over CO_2 production; other abbreviations as in **Tables 1 and 2**.

RESULTS

CLINICAL CHARACTERISTICS. The patients' selection flowchart is depicted in Supplemental Figure 1. All patients were studied in stable clinical conditions and treatment >30 days. In 91% of cases, right heart catheterization was prescribed as part of a routine evaluation of dyspnea. Only 9% of patients were studied for either worsening symptoms or after a HF hospitalization/need of intravenous diuretic agents in the previous 12 months. HFpEF-latentPVD patients represented 21% of our HFpEF cohort who had undergone exercise right heart catheterization.

The clinical characteristics of our study groups are summarized in **Table 2**. They represented a typical elderly, overweight, and predominantly female HFpEF population. HFpEF-latentPVD patients were older (77 years [IQR: 71-81 years] vs 72 years [IQR: 67-78 years]; *P* = 0.025), more frequently had atrial fibrillation (56% vs 29%; *P* = 0.004), and had higher probability of HFpEF based both on the HFA-PEFF

and the H_2FPEF scores (4.8 ± 1.3 vs 3.3 ± 2.0 and 5.1 ± 2.0 vs 3.9 ± 2.0, respectively; *P* < 0.05).

Albeit within normal limits, left ventricular ejection fraction was lower in HFpEF-latentPVD patients than in HFpEF control patients (61% [IQR: 54%-65%] vs 64% [IQR: 62%-66%]; *P* = 0.007). Additionally, HFpEF-latentPVD patients more frequently had at least moderate tricuspid regurgitation (61% vs 28%; *P* = 0.009) and slightly higher estimated systolic pulmonary artery pressure on echocardiography (40 mm Hg [IQR: 35-53 mm Hg] vs 33 mm Hg [IQR: 28-45 mm Hg]; *P* = 0.003).

Natriuretic peptides were not systematically collected, resulting in some missing data for this variable. ProBNP, but not BNP, was higher in HFpEF-latentPVD patients than in HFpEF control patients.

HEMODYNAMICS AND CARDIORESPIRATORY PROFILE. Complete hemodynamic and cardiorespiratory data at rest and during exercise are shown in **Table 3**. In 57% of patients the mean PAWP at rest was <15 mm Hg, including 50% of HFpEF-latentPVD patients and 59%

TABLE 4 Dichotomization of Hemodynamic Profiles at Rest and During Exercise

	Rest			Exercise		
	HFpEF Control Patients	HFpEF-LatentPVD Patients	P Value	HFpEF Control Patients	HFpEF-LatentPVD Patients	P Value
Pulmonary hypertension	32 (47)	13 (72)	0.068	41 (60)	17 (94)	0.005
LA hypertension	27 (40)	9 (50)	0.431	68 (100)	18 (100)	1.000
LA dysfunction	15 (22)	7 (39)	0.146	38 (56)	15 (83)	0.054
Pre-capillary component	7 (10)	13 (72)	<0.001	0 (0)	18 (100)	<0.001
Tricuspid regurgitation	4 (6)	2 (11)	0.601	11 (16)	9 (50)	0.002
Low CO	20 (29)	8 (44)	0.226	8 (12)	6 (33)	0.028
Low CO increase				20 (29)	10 (56)	0.039

Values are n (%). See **Table 1** for resting and exercise threshold definitions.
Abbreviations as in **Tables 1 and 2**.

of HFpEF control patients ($P = 0.501$). When complete hemodynamic data (rest and exercise data together) were reviewed, all hemodynamic variables increased with exercise ($P < 0.01$) with the exception of PVR.

Resting hemodynamics differed between the 2 groups only for mean pulmonary artery pressure and PVR, both of which were higher in HFpEF-latentPVD patients than in HFpEF control patients ($P < 0.05$), at similar PAWP, RAP, CO, and stroke volume values. Even after dichotomization of resting hemodynamic patterns based on preestablished cutoff values (**Table 1**), the 2 groups presented with similar distributions of left atrial hypertension, tall PAWP V waves, higher systolic increase of RAP, and low CO (**Table 4**). Pulmonary hypertension was nonsignificantly more represented in latent PVD (72% vs 47%; $P = 0.068$). Interestingly, more HFpEF-latentPVD patients than HFpEF control patients (72% vs 10%; $P < 0.001$) presented with a precapillary component (PVR >2 WU) at rest. Among the 5 patients with HFpEF-latentPVD and normal PVR at rest (6% of the whole cohort), mean PVR at rest was 1.2 ± 0.4 WU.

The results of exercise hemodynamics were strikingly different between the 2 groups, as shown in **Tables 3 and 4**, Supplemental Table 1, and the **Central Illustration**, at similar levels of heart rate (73% ± 15% of predicted vs 74% ± 13% of predicted in HFpEF-latentPVD patients vs HFpEF control patients; $P = 0.621$) and lactates (4.3 mmoL/L [IQR: 3.5-4.6 mmoL/L] vs 3.7 mmoL/L [IQR: 2.5-5.0 mmoL/L] in HFpEF-latentPVD patients vs HFpEF control patients; $P = 0.648$).

In particular, mean pulmonary artery pressure remained higher in HFpEF-latentPVD patients, despite lower PAWP (**Figure 1**) and a smaller increase in CO and stroke volume (**Figure 2**). In HFpEF-latentPVD patients, stroke volume irrelevantly increased with exercise, from 62 mL to 68 mL. All this

was mirrored by a lack of decrease of PVR in HFpEF-latentPVD patients as compared with HFpEF control patients, in whom PVR physiologically reduced with exercise (**Central Illustration**). Mean RAP and end-diastolic RAP increased to similar values in the 2 groups; however, the RAP systolic component rose more steeply and to higher values in HFpEF-latentPVD patients. Dichotomization of exercise hemodynamic patterns based on preestablished cutoff values (**Table 1**) revealed a higher proportion of pulmonary hypertension, tall PAWP V waves, systolic RAP increase, and low CO in HFpEF-latentPVD patients as compared with HFpEF control patients (**Table 4**).

In regard to cardiorespiratory variables, differences related to the underlying group (HFpEF-latentPVD patients vs HFpEF control patients), to the stage of the test (rest vs exercise), and to their interaction were evident, as shown in **Table 3** and Supplemental Table 1. As expected, all cardiorespiratory variables changed during exercise ($P < 0.05$). VO_2 increased less in HFpEF-latentPVD patients up to lower values at peak exercise, driven by impaired CO response. Peripheral O_2 extraction showed an opposite behavior, increasing more and to higher values in HFpEF-latentPVD patients, mirrored by opposite mixed venous O_2 saturation and mixed venous partial pressure O_2 pressure trajectories. Arterial partial pressure for carbon dioxide ($PaCO_2$) was higher both at rest and at peak exercise in HFpEF-latentPVD patients. Although minute ventilation increased less in HFpEF-latentPVD patients than in HFpEF control patients, the extent of hyperventilation, as reflected by the ratio between minute ventilation and CO_2 production, was similar in the 2 groups. However, this similar extent of hyperventilation at peak exercise occurred at higher dead space ventilation and higher $PaCO_2$ in HFpEF-latentPVD patients.

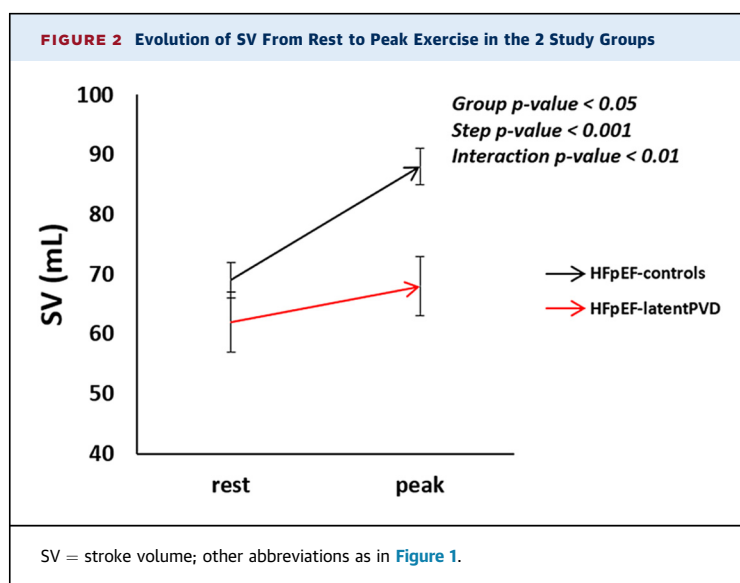**CENTRAL ILLUSTRATION** Hemodynamic and Cardiorespiratory Characteristics of HFpEF-latentPVD Patients
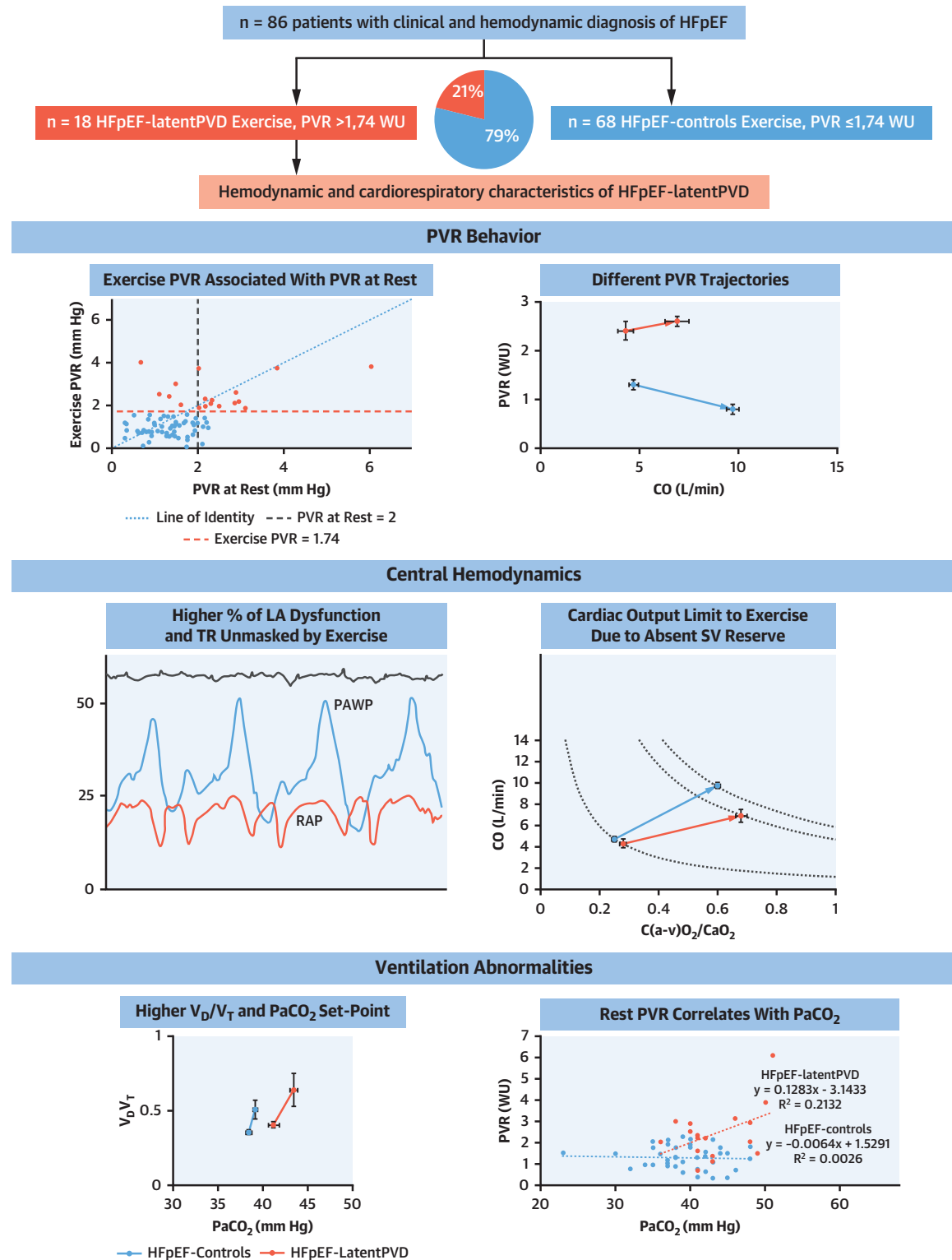
Caravita S, et al. J Am Coll Cardiol HF. 2023;11(10):1427-1438.

C(a-v)O$_2$/CaO$_2$ = peripheral oxygen extraction; CO = cardiac output; HFpEF = heart failure with preserved ejection fraction; LA = left atrium; PaCO$_2$ = arterial partial pressure for carbon dioxide; PAWP = pulmonary artery wedge pressure; PVD = pulmonary vascular disease; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SV = stroke volume; TR = tricuspid regurgitation; V$_D$/V$_T$ = dead space ventilation.

FIGURE 1 Evolution of Pulmonary Pressures From Rest to Peak Exercise in the 2 Study Groups

HFpEF = heart failure with preserved ejection fraction; mPAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVD = pulmonary vascular disease.
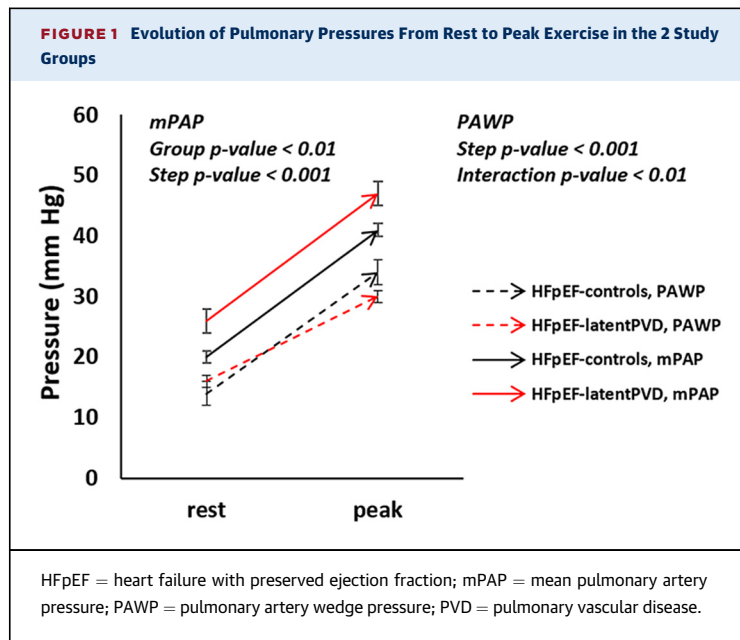
PVR at rest was directly associated with $PaCO_2$ in HFpEF-latentPVD patients only (**Central Illustration**). At peak exercise, PVR was inversely associated with stroke volume and stroke volume index (**Figure 3**) and also with mixed venous O_2 pressure in HFpEF-latentPVD patients only (Supplemental Figure 2).

EVENT-FREE SURVIVAL. During a median follow-up of 1,186 (825-1586) days, 12 patients (6 HFpEF-latentPVD patients and 6 HFpEF control patients) experienced an event. The 3-year event-free survival was 72% in HFpEF-latentPVD patients and 93% in HFpEF control patients (**Figure 4**) (log-rank test $P = 0.004$).
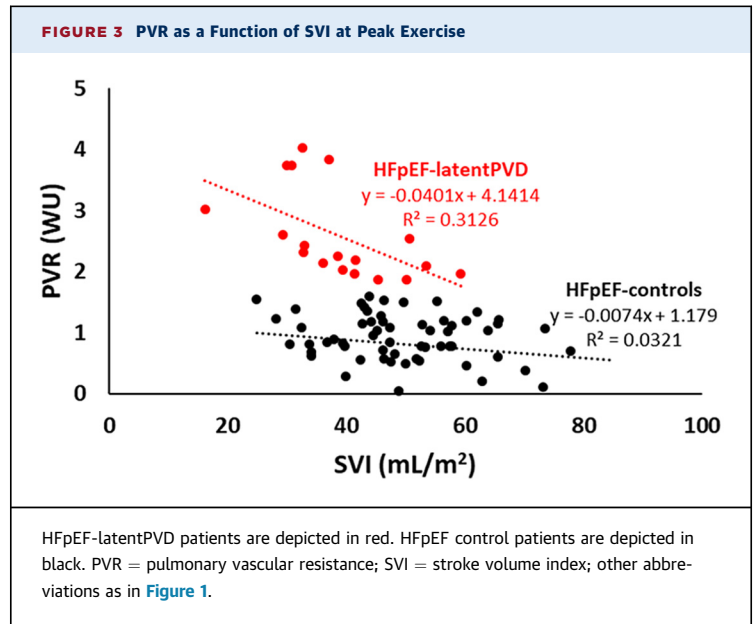
DISCUSSION

Our work provides an in-depth analysis of the HFpEF-latentPVD phenotype and expands on a prior description provided by the REDUCE LAP-HF II study[7] in a real-world, single-center population. First, the HFpEF-latentPVD phenotype was present in 21% of our cohort, but in the great majority of cases (ie, 72%), it could have been anticipated by PVR >2 WU at rest. Thus, PVR did not increase during exercise in most of our HFpEF-latentPVD patients. Additionally, the HFpEF-latentPVD hemodynamic phenotype seems to be associated not only with the severity of the HFpEF profile but also with a steep systolic RAP increase during exercise. This feature suggests the presence of tricuspid regurgitation,[15] whose hemodynamic impact may be missed at rest, becoming overtly evident only during exercise and potentially leading to CO limitation and pulmonary vascular derecruitment with high PVR. Moreover, our results may suggest an increased responsivity of the pulmonary vessels to chemical stimuli (O_2 and CO_2) in patients with HFpEF-latentPVD, who presented with signs of altered ventilatory control, that may further contribute to slightly increased PVR. Finally, and irrespective of the pathophysiology behind the HFpEF-latentPVD profile, an exploratory analysis found this hemodynamic phenotype to be associated with worse prognosis.

In our cohort, the HFpEF-latentPVD phenotype was slightly less frequent than in the REDUCE LAP-HF II trial (21% vs 33%). Additionally, as compared with the REDUCE LAP-HF II trial, very few patients with the HFpEF-latentPVD phenotype (6% of our HFpEF cohort) had isolated latent PVD, ie, normal PVR at rest (<2 WU) that became abnormal (>1.74 WU) during exercise. Potential reasons for these discrepant results, among many similarities between our analysis and the analysis provided by Borlaug et al,[7] may be sought in: 1) the selection of the population under analysis; and 2) the methodology of exercise right heart catheterization. First, as compared with the REDUCE LAP-HF II trial, our patients with HFpEF were more frequently studied as a part of a routine evaluation for dyspnea, with very few of them having experienced worsening HF during the previous year (as compared with 43% of patients enrolled in the REDUCE LAP-HF II), showing lower median natriuretic peptide levels and presenting in about half of cases with PAWP <15 mm Hg (as compared with 29% in the REDUCE LAP-HF II). Thus,

FIGURE 2 Evolution of SV From Rest to Peak Exercise in the 2 Study Groups

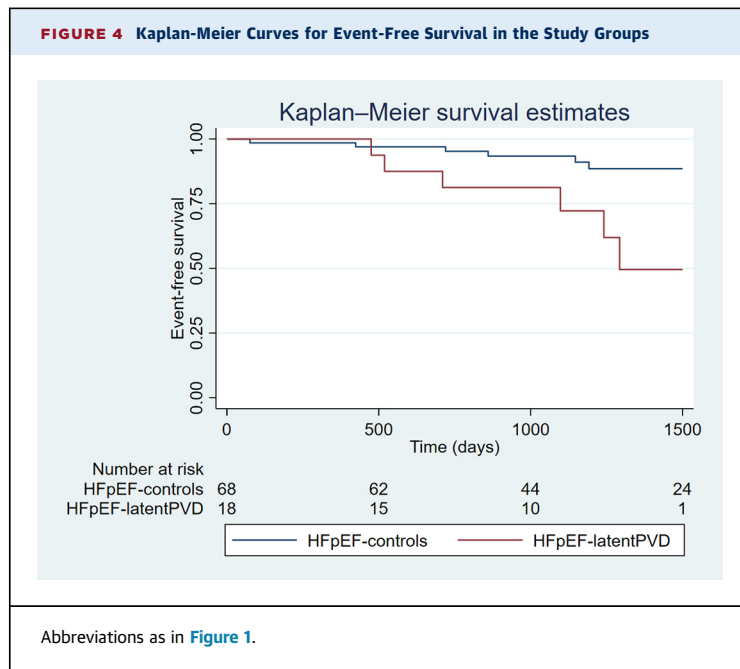SV = stroke volume; other abbreviations as in **Figure 1**.

the more advanced phenotype of patients enrolled in the REDUCE LAP-HF II trial may justify a slightly higher proportion of patients classified as having HFpEF-latentPVD. Second, in the REDUCE LAP-HF II trial,[6] CO was measured by a single-shot thermodilution injection at peak exercise, rather than through 3 sets of measurement with <10% variation, which is the standard during right heart catheterization at rest but may be too time consuming in a dynamic scenario such as at peak effort. It has been already demonstrated that thermodilution may underestimate CO during exercise,[18] thus potentially leading to higher than expected PVR, even though the CO findings in our study and in the REDUCE LAP-HF II trial were comparable. However, by measuring CO by the direct Fick method, we could show a relative stability or decrease of PVR in the great majority of our HFpEF-latentPVD patients as compared with resting values, whereas PVR physiologically decreased in our HFpEF control patients.

As a novelty of our study, which expands the previous evidence generated by the post hoc analysis of the REDUCE LAP-HF II trial,[7] we found that the HFpEF-latentPVD phenotype was associated with tricuspid regurgitation. Indeed, tricuspid regurgitation equal or more than moderate, as evaluated through echocardiography, was present in about one-third of our patients, whereas it was an exclusion criterion for the REDUCE LAP-HF II. Tricuspid regurgitation may frequently complicate HFpEF: Obokata et al[19] previously showed how atrial fibrillation, which is frequent in HFpEF,[20] is associated with biatrial remodeling and tricuspid regurgitation in the population with HFpEF. However, there is scarce information on the behavior of tricuspid regurgitation during exercise in HFpEF and on its hemodynamic impact.[21] Indeed, HFpEF patients, albeit not presenting with overt signs of fluid overload, may harbor increased stressed blood volume (functional preload), magnified by physical exercise.[22,23] On the basis of hemodynamic data (systolic RAP increase),[15] we found that the impact of even moderate or severe tricuspid regurgitation might have been missed at rest (no difference between HFpEF-latentPVD patients and HFpEF control patients in terms of systolic RAP increase in resting conditions) but became overtly evident during exercise, when stressed blood volume is shifted from the splanchnic reservoir to the chest,[22,23] affecting first the right heart and the tricuspid annulus. The tricuspid annulus is a virtual structure, largely composed of adipose tissue, with a smaller amount of fibrotic tissue,[24] potentially predisposing it to pathologic dilation when the right ventricle and/or the right atrium dilate.[25-28] Thus,

FIGURE 3 PVR as a Function of SVI at Peak Exercise

HFpEF-latentPVD
$y = -0.0401x + 4.1414$
$R^2 = 0.3126$

HFpEF-controls
$y = -0.0074x + 1.179$
$R^2 = 0.0321$

HFpEF-latentPVD patients are depicted in red. HFpEF control patients are depicted in black. PVR = pulmonary vascular resistance; SVI = stroke volume index; other abbreviations as in **Figure 1**.

hemodynamically relevant tricuspid regurgitation during exercise, mirrored by a higher systolic RAP increase in HFpEF-latentPVD patients,[15] could help explain an afterload-independent, exercise-induced right ventricular failure. Indeed, the increase in regurgitant volume during exercise would potentially lead to lower forward stroke volume and reduced stroke volume reserve. We may speculate that in the presence of low forward stroke volume, associated with tricuspid regurgitation, CO limitation, and nearly exhausted peripheral O_2 extraction, the low blood O_2 content coming to the pulmonary vessels may favor a certain degree of pulmonary vasoconstriction in HFpEF-latentPVD.[29] This reasoning may partially explain the correlation we found between PVR on one side and stroke volume index as well as mixed venous O_2 pressure on the other side.

As an alternative hypothesis, increased PVR may have contributed to reduced stroke volume and CO in HFpEF-latentPVD patients (as well as to afterload-related tricuspid regurgitation). However, it is important to note that the extent of PVR elevation was mild and relatively stable during exercise in the majority of HFpEF-latentPVD patients and thus was pretty unlikely to cause, per se, right ventricular failure and low CO. HFpEF-latentPVD patients had no stroke volume reserve during exercise and had to rely heavily on peripheral O_2 extraction, whose increase was, however, not enough to compensate for low CO, leading to reduced exercise capacity. In this regard, lower hemoglobin content, once again pointing to a more advanced (and potentially more hemodiluted)

FIGURE 4 Kaplan-Meier Curves for Event-Free Survival in the Study Groups

Kaplan–Meier survival estimates

Abbreviations as in Figure 1.

hypertension as opposed to isolated postcapillary pulmonary hypertension.[32-35] However, in previous studies, combined postcapillary and precapillary pulmonary hypertension was defined on the basis of older definitions, the studies included younger patients, with heterogeneous left heart disease and more severe hemodynamics (higher mean pulmonary artery pressure and PVR), and $PaCO_2$ was rarely collected at rest and/or during exercise, rather relying on its end-expiratory values. Thus, we may speculate that our older HFpEF-latentPVD patients may present with a slightly blunted chemoreflex response to CO_2 and a higher $PaCO_2$ setpoint. Despite this, their exercise hyperventilation was similar to that of their counterparts without latent PVD, likely as a consequence of increased exercise dead space ventilation in latent PVD. This may imply that the simple evaluation of the relationship of minute ventilation over CO_2 production during a noninvasive cardiopulmonary exercise test may not be able to correctly identify HFpEF-latentPVD patients bearing only a minor increase in PVR.

STUDY LIMITATIONS. This was a retrospective study conducted on a limited number of HFpEF patients, and that may limit the generalizability of our results. Additionally, we reported data from a relatively stable outpatient population of HFpEF patients, with relevant differences from those included in the REDUCE LAP-HF II trial; that may in part explain some divergent results, which nonetheless expand the understanding of this peculiar hemodynamic condition. Moreover, it is important to highlight that most of our results were consistent with those reported in the REDUCE LAP-HF II trial[7] (latent PVD being older, with a higher pretest probability of HFpEF based on validated scores, and more atrial fibrillation). Additionally, all tests were conducted and interpreted by the same cardiologists with a specific training in exercise hemodynamics, adopting gold-standard methodology.

Given that patients with isolated latent PVD (PVR <2 WU at rest and >1.74 WU at peak) were only 6% of our cohort, this analysis was unable to determine the clinical and hemodynamic characteristics of this subgroup; rather, we focused on all patients with exercise PVR >1.74 WU.

Again, due to the retrospective nature of our study, echocardiographic characterization of the right heart, which would benefit from a 3-dimensional analysis,[12] was not systematically available, even though it would have added additional insights into the HFpEF-latentPVD phenotype.

HFpEF phenotype, played a role in contributing to a reduction in peak VO_2 in this population.

It is important to point out that other factors may contribute to higher PVR in our HFpEF-latentPVD population. First, we found a higher proportion of patients with pulmonary hypertension during exercise, with a (nonsignificantly) higher proportion of tall V waves in the PAWP position in the HFpEF-latentPVD group. We speculate that a stiffer left atrium in HFpEF-latentPVD patients, which is expected based on the higher proportion of atrial fibrillation,[19] may indeed promote pulmonary vasoconstriction and/or vascular remodeling (including venular congestive remodeling[30]) and high PVR. Second, $PaCO_2$ values were higher in HFpEF-latentPVD patients than in HFpEF control patients both at rest and during exercise, and resting $PaCO_2$ correlated with PVR in HFpEF-latentPVD patients. A relationship of a modest age-related pulmonary comorbidity in HFpEF patients and/or an alteration of ventilatory control (reduced chemosensitivity) with the HFpEF-latentPVD phenotype did not emerge from the analysis of the REDUCE LAP-HF II. Despite the known responsiveness of the pulmonary vessels to CO_2, which has been used to explain precapillary pulmonary hypertension in obesity-hypoventilation syndrome,[31] this finding may appear counterintuitive at first glance, inasmuch as previous evidence pointed to augmented exercise hyperventilation in combined postcapillary and precapillary pulmonary

We relied on hemodynamic signs of tricuspid regurgitation during exercise rather than on its direct echocardiographic visualization. The cutoff of the systolic component of RAP we chose to identify severe tricuspid regurgitation comes from recent evidence that patients undergoing percutaneous tricuspid valve repair and displaying a systolic increase in RAP >8 mm Hg experience poorer outcomes, suggesting procedure failure.[15] Thus, even though this cutoff has still not been validated, it seems to be quite specific for the presence of severe tricuspid regurgitation. Additionally, echocardiographic evaluation of the severity of tricuspid regurgitation requires a multiparametric approach,[13] which might not be easily applicable to exercise studies.

CONCLUSIONS

When CO is measured with the direct Fick method, isolated latent PVD that unmasked only with exercise (PVR <2 WU at rest and >1.74 WU at peak) was uncommon in our HFpEF cohort, whereas the majority of patients with PVR >1.74 WU during exercise already had high PVR (>2 WU) at rest. HFpEF-latentPVD patients presented with reduced right ventricular CO reserve, potentially favored by mildly increased PVR and by dynamic tricuspid regurgitation, whose hemodynamic impact was enhanced by physical exercise. Additional factors, including a more advanced HFpEF phenotype and mild CO_2 retention, this latter suggesting an underlying pulmonary comorbidity and/or an alteration of the ventilatory control, may play a role in pulmonary remodeling and/or vasoconstriction in this population. The clinical, hemodynamic, and cardiorespiratory alterations associated with the HFpEF-latentPVD phenotype may lead to worse event-free survival in this population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: When cardiac output is measured with the direct Fick method, HFpEF with latent PVD (exercise PVR >1.74 WU) may be anticipated in the majority of cases based on PVR >2 WU at rest; isolated latent PVD (rest PVR <2 WU and exercise PVR >1.74 WU) was uncommon. Older HFpEF patients with atrial fibrillation, higher H_2FPEF score, higher estimated systolic pulmonary artery pressure, and at least moderate tricuspid regurgitation are at risk for having latent PVD. The latent PVD profile identifies a small but not negligible proportion of HFpEF patients with more impaired cardiac reserve and exercise limitation, portending a poor prognosis.

TRANSLATIONAL OUTLOOK: Tricuspid regurgitation may dynamically occur or become aggravated during exercise in patients with HFpEF, impairing anterograde stroke volume and thus potentially contributing to the latent PVD profile (ie, contributing to a factitious PVR increase caused by pulmonary vascular derecruitment). Studies combining advanced hemodynamics and advanced echocardiography are warranted to better understand the dynamicity of tricuspid regurgitation and right heart adaptation to exercise in HFpEF patients. The precapillary component of right ventricular afterload appears to be more a consequence of the underlying disease and comorbidities, suggesting that the use of treatments targeting the pulmonary circulation may not be effective in this setting.

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KEY WORDS exercise, heart failure, pulmonary hypertension, right heart catheterization, tricuspid regurgitation

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APPENDIX For supplemental figures and a table, please see the online version of this paper.