Pulmonary Circulation

WILEY | PVRi

RESEARCH ARTICLE OPEN ACCESS

Hemodynamic-Driven Staging of Heart Failure With Preserved Ejection Fraction Using Unsupervised Cluster Analysis

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Received: 7 May 2025 | **Revised:** 30 December 2025 | **Accepted:** 4 February 2026

Funding: Ministero dell'Università e della Ricerca, Grant/Award Number: PNC0000003-AdvaNcedTechnologiesforHuman-centrEdMedicine(ANTHEM)

Keywords: cluster analysis | heart failure | hemodynamics | pulmonary hypertension | tricuspid regurgitation

ABSTRACT

Invasive exercise hemodynamics are used to diagnose heart failure with preserved ejection fraction (HFpEF), based on pulmonary artery wedge pressure (PAWP) or left atrial (LA) pressure elevations. We hypothesized that applying unsupervised cluster analysis to comprehensive hemodynamic characterization might provide data-driven phenotypes, with pathophysiological and prognostic implications. Eighty consecutive HFpEF patients underwent right heart catheterization at rest, during passive leg raise, and at peak exercise. We performed unsupervised *k*-means clustering analysis, using eight hemodynamic variables that were not strongly correlated (Pearson correlation coefficient < 0.80). Hemodynamics and clinical characteristics, as well as event-free survival, were assessed. $k = 5$ clusters were identified. Hemodynamic severity increased from Cluster 1 to Clusters 4–5 ($p < 0.01$ for most of the hemodynamic variables), mirrored by different event-free survival (log-rank test $p < 0.001$). Clusters 1 and 2 presented with either steep PAWP rise or LA hypertension and pulmonary hypertension (PH) only during exercise. Cluster 3 presented with LA hypertension and PH already at rest, as well as with tall PAWP V waves during exercise. Cluster 4 presented with post- and precapillary PH, tall PAWP V waves, right atrial (RA) hypertension, dynamic tricuspid regurgitation (TR), and low cardiac output (CO) reserve. Cluster 5 presented with TR and RA hypertension, low CO, and a lack of decrease in PVR. Data-driven unsupervised cluster analysis of advanced invasive hemodynamics allowed for the identification of distinct HFpEF phenotypes across the spectrum of disease severity. We found a progressive involvement of the pulmonary circulation and of the right heart, coupled with a worse prognosis.

Abbreviations: CO, cardiac output; HF, heart failure; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; HFA-PEFF, heart failure association-pretest assessment, echocardiographic and natriuretic peptide score, functional testing in case of uncertainty, etiological workup; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PH, pulmonary hypertension; RA, right atrium; RAP, right atrial pressure; PVD, pulmonary vascular disease; RHC, right heart catheterization; VO_2, oxygen consumption.

1 | Background

Exercise hemodynamics is increasingly used to diagnose heart failure (HF) with preserved ejection fraction (HFpEF) [1]. In particular, the behavior of pulmonary artery wedge pressure (PAWP), as a surrogate for left atrial (LA) pressure, has been advocated as the more sensitive marker of this disease [2, 3]. Indeed, a steep PAWP increase is consistent with the pathophysiological definition of HF, that is, the inability of the left heart to cope with increasing metabolic demands but at the expense of high filling pressure [3]. This definition helps to unify the heterogeneous HFpEF syndrome, reconducting exertional symptoms to a primary cardiac abnormality. Nonetheless, a steep PAWP rise may underscore distinct abnormalities, such as increased left ventricular (LV) stiffness [4] and/or LA myopathy [5, 6] and/or enhanced ventricular interdependence in obese HFpEF. Additionally, even if HFpEF is primarily a disease of the left heart, it is frequently complicated by right heart involvement (including pulmonary hypertension, PH; right ventricular dysfunction; tricuspid regurgitation, TR), through afterload-dependent and afterload-independent mechanisms [7–9]. Since exercise right heart catheterization (RHC) dynamically captures many more variables than PAWP alone, it may provide deeper insights into individuals' pathophysiology. We hypothesized that using unsupervised clustering analysis on the hemodynamic data from HFpEF patients at rest, during leg raise, and exercise can reveal unique hemodynamic patterns, indicate various levels of disease severity, predict event-free-survival, and suggest treatment options based on the underlying physiology.

2 | Methods

This study was approved by the local Ethics Committee (protocol n 2022_09_27_01 approved on September 27, 2022). We retrospectively analyzed data from patients who underwent an elective rest and exercise RHC between August 2018 and March 2021 at Ospedale San Luca IRCCS Istituto Auxologico Italiano, Milan, Italy. Common indications for RHC at our center are unexplained dyspnea, suspicion of HFpEF, and PH. This cohort is in partial overlap with those published in other studies from our center [10–14].

We only included patients who fulfilled the hemodynamic criteria for HFpEF, that is, a PAWP at rest > 15 mmHg and/or a PAWP at peak exercise ≥ 25 mmHg and/or a PAWP/cardiac output (CO) slope > 2 mmHg/L/min [2, 3, 11].

We excluded patients with reduced left ventricular ejection fraction (LVEF < 50%), infiltrative cardiac disease, pericardial constriction, congenital heart disease (either corrected or uncorrected), primary valvular heart disease, pulmonary vascular disease (PVD) such as pulmonary arterial hypertension and chronic thromboembolic PH or chronic thromboembolic pulmonary disease. Accordingly, no patient was treated with pulmonary arterial hypertension-specific drugs.

Clinical data obtained in the week before RHC were similarly collected, given that no changes in clinical conditions or treatment had occurred. Clinical data were used to calculate the H_2FPEF (heavy, hypertensive, atrial fibrillation, PH, elder, filling pressure) [15] and HFA-PEFF scores (HF association-pretest assessment, echocardiographic and natriuretic peptide score, functional testing in case of uncertainty, etiological workup) [16]. Follow-up and outcome data after RHC, including cardiovascular hospitalizations, need for intravenous diuretics, and death, were retrieved from medical charts.

2.1 | Right Heart Catheterization

RHC was conducted in nonsedated and nonfasting patients, in the supine position. A 7 F Swan-Ganz catheter was positioned in the pulmonary artery (PA) through the internal jugular vein under local anesthesia and under ultrasound guidance. The radial artery was cannulated by the Seldinger's technique. The transducers were zeroed at midthoracic level. Patients wore a non-rebreathing mask connected to the VMAX metabolic cart for the direct measurement of oxygen consumption (VO_2).

Hemodynamic and gas-exchange measures were performed at rest, 1 min after having positioned the patients' feet on the pedals, and during the last minute of several exercise steps. At each step, 2 mL of blood was drawn both by the PA and by the radial artery. The step-incremental protocol was personalized, aiming to reach maximal volitional effort in about 6–12 min [10, 11].

PA pressures, PAWP, and right atrial (RA) pressure (RAP) were offline reviewed by two experienced readers, and reflect the end-expiratory average of several respiratory cycles [10, 11]. The subcomponents of PAWP and RAP waveforms were measured [11]. PAWP V wave amplitude was computed as the difference between the zenith of the V wave and the mean PAWP [11]. RAP systolic amplitude was computed as the difference between the zenith of the V wave and the diastolic through [10, 17]. CO was measured by the direct Fick's method by integrating VO_2 and arteriovenous difference. CO was indexed for body surface area to obtain cardiac index. A linear regression was applied to pressure-flow relationship built with either mean PA pressure, PAWP, or RAP as the dependent variable and CO as the independent variable. Pulmonary vascular resistance (PVR) was calculated as (mean PA pressure–mean PAWP)/CO.

LA hypertension at rest was defined by a PAWP > 15 mmHg, while during exercise by a PAWP ≥ 25 mmHg [2, 10, 18]. A stiff LA (or LA myopathy) was defined by the presence of PAWP V wave amplitude > 10 mmHg [10, 11]. A steep PAWP rise was defined as a PAWP/CO slope > 2 [1, 3, 11]. PH was defined at rest by a mean PA pressure > 20 mmHg, while during exercise as a mean PA pressure/CO slope > 3 mmHg/L/min [19]. Low CO at rest was defined as a cardiac index < 2 L/min/m^2 and during exercise as a CO/VO_2 slope < 4.7. The presence of a precapillary component was defined at rest by PVR > 2 WU (codifying combined post- and precapillary PH) [19], and during exercise by PVR > 1.74 WU (latent PVD phenotype) [10, 20]. RA hypertension was defined at rest by a RAP > 8 mmHg, while during exercise by a RAP > 12 mmHg [8]. A steep RAP rise was defined as a RAP/CO slope > 1.2 mmHg/L/min [8]. The presence of hemodynamically significant TR and/or RA myopathy was defined at rest and during exercise by a RAP systolic amplitude > 8 mmHg [10, 17, 21].

2.2 | Cluster Analysis

Before proceeding to cluster analysis, we evaluated the correlation between the considered hemodynamic metrics, regardless of exercise step: mean PA pressure, mean PA pressure/CO

slope, end-diastolic PAWP, PAWP V amplitude, mean PAWP, PAWP/CO slope, PVR, end-diastolic RAP, mean RAP, RAP systolic amplitude, RAP/CO slope, cardiac index, and CO/VO_2 slope. Anticipating large collinearity among hemodynamic variables, we planned to perform cluster analysis using those hemodynamic variables that would lack high correlation (Pearson correlation coefficient < 0.80). In case of high correlation between two variables, we planned to prefer PAWP (as *the* marker of HFpEF) over PA pressure and RAP and to prioritize values averaged throughout the cardiac cycle over end-diastolic or systolic values.

To perform the cluster analysis, we adopted the *k*-means clustering method, with the Euclidean distance on the actual measurements without further normalization.

2.3 | Statistical Analysis

The hemodynamic metrics (also those excluded from the generation of the clusters) and other patient features were analyzed over the obtained clusters. Continuous variables were reported as median (1st–3rd quartile), while binary and categorical variables are shown as absolute frequencies and proportions.

Between clusters differences were evaluated with the two-sided Kruskal–Wallis test for continuous variables, and with the two-sided chi-squared test for binary and categorical variables. Statistical significance was set at the 0.05 level.

Kaplan–Meier curves were used to estimate the event-free (cardiovascular hospitalizations, need for intravenous diuretics, and death) survival rates in the different patients' clusters, and, in an exploratory analysis, the differences between groups were evaluated through the log-rank test.

All analyses were performed with R Core Team (2021, Vienna, Austria).

3 | Results

Data from 80 HFpEF patients were retrieved. The correlation between the 14 hemodynamic variables is reported in Table S1. Based on this, eight of 14 hemodynamic variables that did not result in highly correlated (Pearson correlation coefficient < 0.80) were chosen for cluster analysis: mean PAWP, PAWP V amplitude, PAWP/CO slope, mean PA pressure/CO slope, RAP systolic amplitude, PVR, cardiac index, and CO/VO_2 slope.

3.1 | Hemodynamic Clusters

Figure S1 reports the within-cluster sum of squares as a function of the number of clusters, which shows an elbow, although not very pronounced, at about five clusters. Therefore, $k = 5$ was set as the number of clusters.

Table 1 shows the complete hemodynamic data, at rest and during exercise, for each of the five identified HFpEF hemodynamic clusters. Table 2 offers a clinical interpretation of the hemodynamic data for each cluster.

As shown, Cluster 1 ($n = 26$) presented a minimal hemodynamic compromise. The only hemodynamic variable that, in median, could be interpreted as abnormal was PAWP/CO slope. Cluster 2 ($n = 30$) presented with borderline PAWP at rest and during feet on pedals, becoming abnormal during exercise, as well as a PAWP/CO slope > 2 mmHg/L/min. Similarly, mean PA pressure was borderline at rest, but the mean PA pressure/CO slope during exercise was > 3 mmHg. Cluster 3 ($n = 12$) presented a median with PAWP > 15 mmHg at rest and > 25 mmHg during exercise, mean PA pressure > 20 mmHg at rest, and mean PA pressure/CO slope > 3 mmHg/L/min during exercise. Additionally, Cluster 3 presented a median with PAWP V wave amplitude > 10 mmHg only during exercise, as well as RAP > 12 mmHg during exercise. Cluster 4 ($n = 4$) presented with an even more severe profile of Cluster 3, showing also a PVR at rest > 2 WU, a RAP at rest > 8 mmHg, a CO/VO2 slope < 4.7, and a RAP systolic amplitude > 8 mmHg during exercise. Cluster 5 ($n = 8$) did not present a median with PAWP V wave amplitude > 10 mmHg, neither at rest nor during exercise, but displayed a cardiac index < 2.2 L/min/m^2 at rest, a PVR > 1.74 WU during exercise, and a RA systolic amplitude > 8 mmHg already at rest.

Coherently, with an increase of hemodynamic derangements from Cluster 1 to Cluster 4 and 5, almost all hemodynamic variables significantly differed across clusters, with the exception of cardiac index at rest, PAWP/CO slope, and mean PA pressure/CO slope.

3.2 | Clinical Characteristics

Table 3 shows the clinical characteristics of the five hemodynamic HFpEF clusters. Age increased from Cluster 1 to Cluster 5, while the female/male sex distribution decreased from Cluster 1 to Cluster 5 ($p < 0.01$). Atrial fibrillation was highly prevalent in Clusters 4 and 5 ($p < 0.01$). The prevalence of diabetes mellitus increased from Cluster 1 to Clusters 4 and 5 ($p < 0.05$). NTproBNP and estimated systolic PA pressure increased from Cluster 1 to Clusters 4 and 5 ($p < 0.01$), while LV ejection fraction showed an opposite behavior. TR $\geq$ moderate was highly prevalent in Clusters 4 and 5, while barely represented in the other clusters. Cluster 4 had the largest LA volume index. Clusters 1 and 2 had the lower E/e' as well as the lower HFA-PEFF and H2FPEF scores ($p < 0.01$). Diuretic use became increasingly more prevalent from Cluster 1 to Clusters 4 and 5.

3.3 | Event-Free Survival

During a follow-up of 1424 (1087–1811) days, 17 events were recorded. Event-free survival differed among the five clusters (Figure 1; log-rank test $p < 0.001$), with Clusters 1 and 2 presenting with better outcomes (two events in each cluster, while the expected number of events would have been of 6.78 and 6.47, respectively), while Clusters 4 and 5 presenting with worse outcomes (four and five events in each cluster, while the expected number of events would have been of 0.86 and 0.85, respectively).

4 | Discussion

With this analysis, we provide a first tentative staging of HFpEF, based on unsupervised cluster analysis of comprehensive hemodynamic data at rest, during passive leg raising, and

TABLE 1 | Hemodynamics at rest, with feet on the pedals, and at peak exercise in the five clusters of patients.

Hemodynamics	Cluster 1 $N = 26$	Cluster 2 $N = 30$	Cluster 3 $N = 12$	Cluster 4 $N = 4$	Cluster 5 $N = 8$	*p*-value
Rest						
PAWP, mmHg	7.5 (6–9)	13 (11.2–16)	20.5 (18–29.5)	19 (17.3–19.5)	22 (18–26.5)	< 0.001
PAWP V wave ampl, mmHg	1 (0.3–2)	1.5 (0–3)	8.5 (2.8–11.5)	14.5 (11–18)	7.5 (6.5–-8.8)	< 0.001
mPAP, mmHg	13.8 (10.3–16.3)	20.5 (18–24)	27 (23–32)	25.5 (21.5–29.5)	30.7 (27.6–33.1)	< 0.001
CI, L/min/m^2	2.57 (2.29–2.95)	2.55 (2.15–2.97)	2.38 (2.02–2.84)	2.41 (2.11–2.58)	1.88 (1.77–2.50)	0.24
PVR, WU	1.34 (1.00–1.66)	1.60 (1.45–1.92)	0.99 (0.57–1.22)	2.11 (1.61–2.36)	1.73 (1.33–2.00)	0.008
RAP, mmHg	3 (1.3–5)	7 (5.3–8)	7 (5.8–9.2)	9.5 (6.8–11.8)	12.5 (9.8–15)	< 0.001
RAP systolic ampl, mmHg	1 (1–2)	1 (1–2)	1 (1–2)	4 (2.3–6.3)	10 (3–12)	0.001
Feet on pedals						
PAWP, mmHg	12 (9.3–13)	18 (16–22.8)	32 (30.3–35.8)	22 (19.3–25.3)	24.5 (22.3–27.8)	< 0.001
PAWP V wave ampl, mmHg	2 (1.3–3)	4 (2.3–5.8)	12.5 (9–18)	14.5 (13.5–17)	7 (7–10.5)	< 0.001
mPAP, mmHg	17.3 (15.6–19.3)	27.8 (24.4–31.2)	35.5 (30.3–38.8)	28.8 (26.3–30.8)	33.5 (30-9–30.5)	< 0.001
CI, L/min/m^2	2.78 (2.51–3.27)	3.09 (2.57–3.46)	1.87 (1.69–2.48)	2.29 (2.04–2.54)	1.86 (1.80–2.15)	0.002
PVR, WU	1.36 (0.86–1.58)	1.49 (0.98–1.90)	0.86 (0.34–1.81)	1.44 (0.28–2.56)	2.10 (1.60–2.55)	0.025
RAP, mmHg	5 (3–6.8)	10.5 (8–11)	11.5 (10.8–14.3)	12.5 (8.5–16)	17 (13–19)	< 0.001
RAP systolic ampl, mmHg	1 (0.3–2)	2 (1–4)	3 (1–4.3)	5.5 (2.3–8.3)	11 (7.3–13.5)	< 0.001
Exercise						
PAWP/CO slope, mmHg/L/min	2.22 (1.73–3.34)	4.04 (2.93–4.85)	3.07 (2.33–4.14)	6.34 (4.55–8.12)	2.26 (1.58–4.31)	0.09
PAWP, mmHg	23 (17.3–26)	34 (31–39.8)	46 (40–50)	32 (27–36.5)	29 (28–31.3)	< 0.001
PAWP V wave ampl, mmHg	5.5 (3.3–6.8)	6 (4–9)	15.5 (13–20)	21.5 (20.8–23.4)	7.5 (5.8–9.3)	< 0.001
mPAP, mmHg	32.2 (27.3–37.3)	43.3 (40.4–49.8)	54.3 (40.3–60.1)	37.8 (36.6–38.3)	41.5 (37.9–52.6)	< 0.001
mPAP/CO slope, mmHg/L/min	2.83 (2.16–4.47)	4.73 (3.31–5.45)	4.26 (2.85–5.13)	5.05 (4.36–6.11)	4.62 (1.89–4.62)	0.07
CI, L/min/m^2	5.66 (4.50–6.28)	5.25 (4.43–6.20)	4.88 (4.22–5.96)	3.31 (3.08–3.74)	3.36 (3.21–4.02)	< 0.001
CO/VO_2 slope	5.76 (4.85–6.86)	5.29 (3.95–5.94)	5.73 (4.47–6.15)	3.39 (2.67–4.11)	3.18 (2.59–5.27)	0.039
PVR, WU	0.96 (0.61–1.27)	1.03 (0.67–1.47)	0.86 (0.70–1.19)	0.96 (−0.16–2.0)	2.29 (1.33–3.76)	0.036
RAP, mmHg	10 (6–13)	18 (14–20)	22 (17.8–24)	22.5 (20.8–24)	25.5 (20.8–27)	< 0.001
RAP/CO slope, mmHg/L/min	1.10 (0.53–1.85)	1.86 (1.27–2.64)	2.07 (1.38–2.45)	5.00 (4.29–6.73)	3.72 (1.58–5.17)	< 0.001
RAP systolic ampl, mmHg	3 (2–4)	5 (2.3–7.8)	4.5 (2–5.3)	17.5 (16.5–22)	16.5 (14.3–21.3)	< 0.001

Note: Abbreviations: Ampl, amplitude; CI, cardiac index; CO, cardiac output; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

TABLE 2 | Visual codification of the five hemodynamic clusters.

		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Clinical Features	Sex	Female predominance	Female predominance	Males = females	Males = females	Male predominance
	Rhythm	Sinus rhythm	Sinus rhythm	Sinus rhythm/ paroxysmal AFib	AFib	Afib
	NTproBNP	Low	Intermediate-low	Intermediate-high	High	High
	HFpEF scores	Low	Intermediate	High	High	High
Hemodynamics	Left atrium	Steep LA pressure rise	Exercise LAH	LAH	LAH	LAH
	Pulmonary circulation	Non-stiff LA	Non-stiff LA	Latent stiff LA	Stiff LA	LA underfilling
		No PH	Exercise PH	PH	PH	PH
		Normal CO	Normal CO	Normal CO	Low CO reserve	Low CO
		Normal PVR	Normal PVR	Normal PVR	CpcPH	Latent PVD
	RIght Atrium	No RAH	Exercise RAH	Exercise RAH	RAH	RAH
		Non-stiff RA/no TR	Non-stiff RA/no TR	Non-stiff RA/no TR	Latent RA myopathy/TR	RA myopathy/TR

Note: Green, low risk characteristics; orange, intermediate risk characteristics; red, high risk characteristics. In particular, for hemodynamics variables only, green color identifies the lack of abnormalities both at rest and during exercise, orange identifies abnormalities only during exercise, and red identifies abnormalities evident already at rest.

Abbreviations: AFib, atrial fibrillation; CpcPH, combined post- and precapillary pulmonary hypertension; CO, cardiac output; LA, left atrium; LAH, left atrial hypertension; PH, pulmonary hypertension; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RA, right atrium; RAH, right atrial hypertension; TR, tricuspid regurgitation.

during exercise. Indeed, our results could identify a clear progression of disease severity spanning from minimal left heart abnormalities to involvement of the pulmonary circulation and of the right heart, with potential prognostic implications (Central Illustration).

These results mirror the current paradigm of HFpEF progression, from an isolated left heart disease to right HF [22, 23]. The novelty here is the way we obtained such results, that is, by means of unsupervised partition of carefully obtained and analyzed individual hemodynamic data during provocative testing in the cath lab. Indeed, by considering a finite number of hemodynamic variables potentially bearing complementary information (i.e., non-highly interrelated), patients were positioned in a hyperspace and grouped based on their similarity, in terms of distance from the center (or centroid) of each cluster. Henceforth, a newly evaluated patient could be classified based on the median hemodynamic values we obtained from each cluster. Among clinical, noninvasive variables, age, sex, atrial fibrillation, LV diastolic dysfunction severity, estimated systolic PAP, natriuretic peptides, and noninvasive scores, the presence of ≥ moderate TR could at least in part anticipate the hemodynamic clusters. However, in-depth hemodynamic phenotyping revealed additional information, overcoming partial overlap between clinical variables.

4.1 | Cluster Analysis in HFpEF and PH

Cluster analysis is increasingly used to seek to decipher HFpEF complexity. A large dataset of HFpEF patients, such as those from the Swedish Heart Failure Registry ($n = 6909$), has been analyzed with latent class analysis to unbiasedly derive five HFpEF phenotypic clusters, with different representations of comorbidities and risk of adverse outcome [24]. A recent study by Larson et al. [25] adopted a different approach. The authors arbitrarily defined pathophysiologically sound phenogroups based on clinical and/or hemodynamic abnormalities: cardiometabolic (body mass index > 30 Kg/m^2 or diabetes mellitus), LA myopathy (LA volume index > 34 mL/m^2 or any history of atrial fibrillation), PVD (mean PA pressure > 20 mmHg and PVR > 2 WU), and vascular stiffening (pulse pressure > 90 mmHg or total arterial compliance index < 0.5 mL/m^2/mmHg). These phenogroups were not mutually exclusive, as one patient could satisfy none, one, or more of the above-mentioned definitions; also, non-HFpEF patients were included and, most of all, phenogroups were defined a priori. Nonetheless, in a cohort of 643 hemodynamically-proven HFpEF patients and 219 patients with noncardiac dyspnea, a larger degree of phenogroups overlap in one individual patient was associated with exercise limitation, worsening hemodynamic perturbations, and conferred a higher risk of adverse outcome. A more unbiased, data-driven approach has been recently employed in 190 patients with PH from various etiologies [26]. Indeed, Janowski et al. identified five clusters of patients starting from a few high-quality, non-highly collinear right ventricular metrics: right ventricular-PA coupling, right ventricular end-systolic elastance, and right ventricular diastolic function. They could thus describe distinct right ventricular behaviors across this heterogeneous cohort of patients. This approach was similar to that employed in our study: starting from non-highly collinear hemodynamic variables collected during different steps of a

TABLE 3 | Clinical characteristics of the five clusters of patients.

	Cluster 1 ($n = 26$)	Cluster 2 ($n = 30$)	Cluster 3 ($n = 12$)	Cluster 4 ($n = 4$)	Cluster 5 ($n = 8$)	*p*-value
General characteristics						
Age, years	68 (60–78)	72 (65–74)	75 (71–79)	76 (72–80)	81 (75–82)	0.0055
Females, *n* (%)	21 (81)	21 (70)	6 (50)	2 (50)	3 (37.5)	0.001
BMI, Kg/m^2	25.3 (22.0–26.6)	27.6 (24.6–32.4)	26.4 (24.5–28.4)	28.0 (25.3–29.1)	28.4 (22.4–29.2)	0.13
Rhythm						< 0.001
Sinus rhythm, *n* (%)	25 (96)	29 (97)	11 (92)	1 (25)	1 (12.5)	
Paroxysmal AFib, *n* (%)	3 (11.5)	4 (13)	3 (25)	1 (25)	1 (12.5)	
Permanent AFib, *n* (%)	1 (4)	1 (3)	1 (8)	3 (75)	6 (87.5)	
Diuretic therapy, *n* (%)	6 (23)	15 (50)	7 (58)	4 (100)	8 (100)	< 0.001
Antihypertensive therapy, *n* (%)	19 (73)	24 (80)	8 (67)	3 (75)	6 (75)	0.906
Pace-maker, *n* (%)	3 (11.5)	0 (0)	3 (25)	3 (75)	2 (25)	0.0005
Obesity, *n* (%)	2 (8)	11 (37)	3 (25)	1 (25)	2 (25)	0.031
Arterial Hypertension, *n* (%)	21 (81)	24 (80)	8 (67)	4 (100)	5 (62.5)	0.002
Diabetes mellitus, *n* (%)	2 (8)	1 (3)	2 (17)	1 (25)	2 (25)	0.015
Coronary artery disease, *n* (%)	2 (8)	5 (17)	4 (33)	1 (25)	2 (25)	0.003
COPD, *n* (%)	6 (23)	8 (27)	4 (33)	2 (50)	0 (0)	0.002
Blood tests						
Hemoglobin, g/dL	13.1 (12.2–14.5)	13.4 (12.6–14.4)	12.8 (12.5–14.1)	11.3 (11.0–11.9)	13.1 (11.1–14.5)	0.33
Creatinine, mg/dL	0.84 (0.76–0.93)	0.96 (0.76–1.06)	0.99 (0.94–1.06)	1.14 (0.98–1.20)	1.02 (0.83–1.13)	0.21
NTproBNP, pg/mL	65 (47–140)	261 (48–546)	561 (298–1104)	978 (164–2142)	755 (734–818)	0.002
Echocardiography						
LV ejection fraction, %	63 (61–64)	64 (62–66)	64 (57–66)	60 (57–63)	54 (53–61)	0.018
LV mass index, g/m^2	89 (74–97)	75 (72–98)	99 (95–107)	105 (80–127)	78 (78–85)	0.11
LAVI, mL/m^2	31 (23–36)	31 (26–41)	50 (40–54)	60 (48–71)	51 (47–66)	< 0.001
E/e'	8 (7–12)	10 (8–11)	13 (12–14)	—	14 (8–15)	0.02
Estimated sPAP, mmHg	26 (30–35)	34 (30–41)	48 (35–53)	51 (44–56)	50 (40–53)	0.008
≥ moderate TR, *n* (%)	2 (8)	2 (7)	1 (8)	3 (75)	6 (75)	< 0.001
HFpEF scores						
H_2FPEF score	3 (2–4)	4 (3–5)	6 (5–6)	6 (6–7)	6 (5–7)	< 0.001
HFA-PEFF score	2 (1–4)	4 (2–5)	6 (5–6)	5 (4–5)	5 (3–6)	0.002

Abbreviations: AFib, atrial fibrillation; COPD, chronic obstructive pulmonary disease; HFA-PEFF, heart failure association-pretest assessment, echocardiographic and natriuretic peptide score, functional testing in case of uncertainty, etiological workup; H_2FPEF, heavy, hypertensive, atrial fibrillation, pulmonary hypertension, elder, filling pressure; HFpEF, heart failure with preserved ejection fraction; LAVI, left atrial volume index; LV, left ventricle; NTproBNP, N-terminal pro brain natriuretic peptide; MR, mitral regigrigation; sPAP, systolic pulmonary artery pressure; TR, tricuspid regurgitation.

dynamic RHC, we identified five clusters of HFpEF patients characterized by progressive disease severity and right heart involvement.

4.1.1 | *Cluster Analysis Based on Resting and Exercise Hemodynamics: Depicting the Natural History of HFpEF*

The HFpEF starting point is LV diastolic dysfunction [2, 4]. Since LV stiffening may be associated with a transient, stress-induced increase in left heart filling pressure, provocative tests are increasingly used to diagnose and phenotype HFpEF patients [27]. A stiff LV may lead to either a steep LA rise or LA hypertension only during exercise, even in the absence of LA dilation, and in the absence of tall V waves in the PAWP position, as was the case in Clusters 1 and 2. These patients were younger, had few comorbidities, were generally in sinus rhythm, had low or relatively low natriuretic peptide levels, may not satisfy the current noninvasive diagnostic criteria for

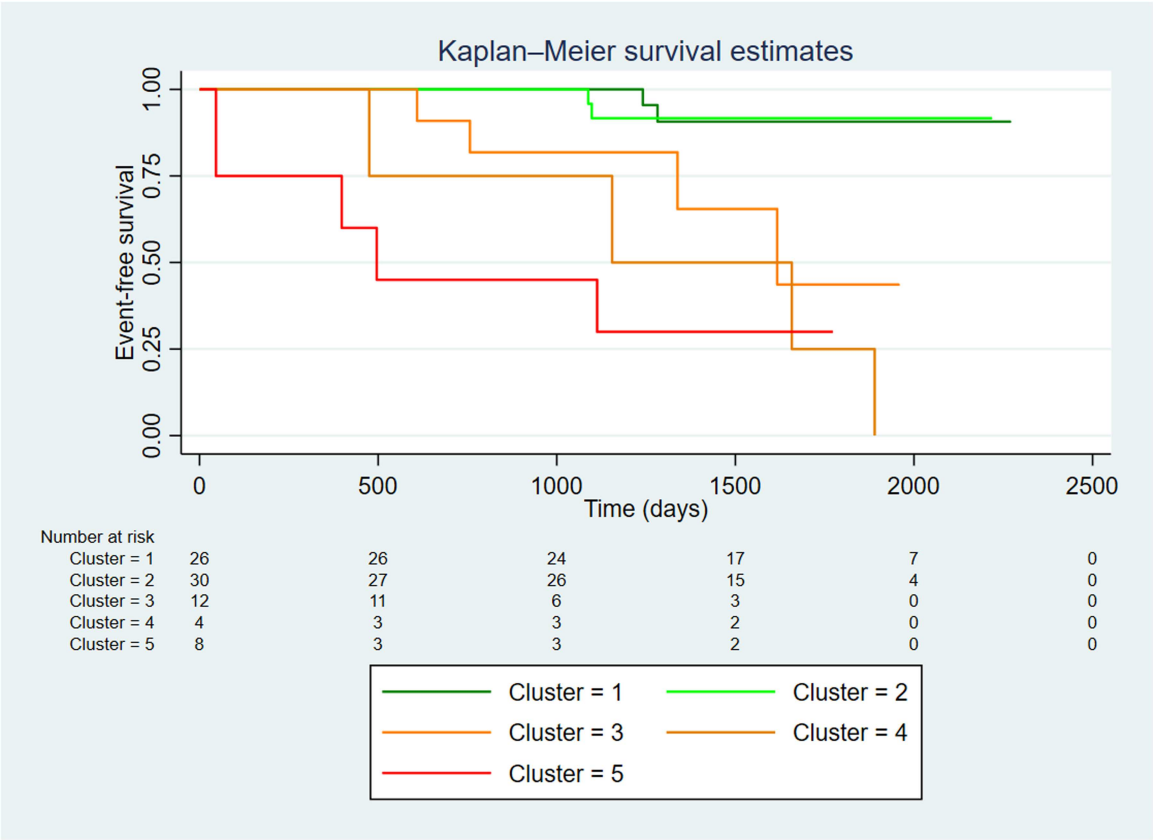
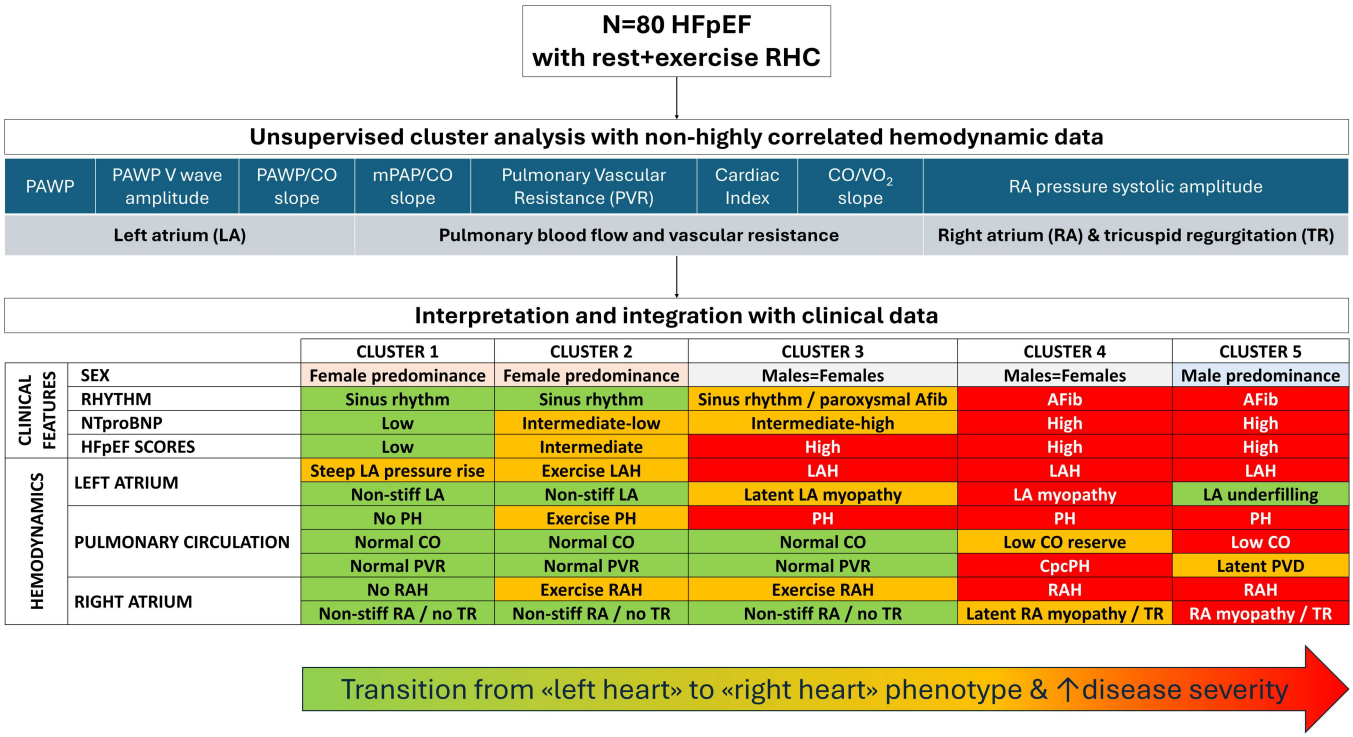


FIGURE 1 | Kaplan–Meier curves for event-free survival in the five clusters of patients.

HFpEF (low or intermediate H_2FPEF and HFA-PEFF scores) [11, 13], and had no signs of pulmonary circulation and right heart involvement. Coherently, they constituted the largest part of our cohort, who may undergo RHC for diagnostic purposes. Curiously, the majority of patients belonging to Clusters 1 and 2 were females. More sensitive noninvasive diagnostic tools would be advisable to intercept these patients in these early phases of symptomatic disease, in order to limit invasive examinations, and to implement lifestyle or pharmacological treatment to prevent disease progression. Additionally, patients from Cluster 2 may qualify for LA shunting devices as an innovative way to palliate disabling exertional symptoms [28].

Over the course of the disease, LA hypertension and PH may intervene at rest. This was the case of Clusters 3–5, albeit with notable differences between them, both on hemodynamic and clinical grounds. Clinically, patients in Clusters 3–5 had in median pathological noninvasive scores as well as higher, although widely dispersed, NTproBNP levels, overt diastolic dysfunction with enlarged LA and high echocardiographic probability of PH. Female sex was equally represented in Clusters 3 and 4, while Cluster 5 presented with a male predominance. The rate of paroxysmal and permanent atrial fibrillation increased from Cluster 3 to Clusters 4 and 5, as the prevalence of moderate or severe TR, reinforcing the pathophysiological link between atrial tachyarrhythmias and RA remodeling [29–31]. Coherently, with LA dysfunction underlying atrial fibrillation, patients in Cluster 3 presented with tall V waves in the PAWP position during exercise. Indeed, exercise-induced sympathetic activation is thought to drive splanchnic venoconstriction, increasing stressed blood volume [32], thus functionally stretching the LA, with an upward shift of its pressure-volume relationship [33]. Nonetheless, patients in Cluster 3 presented with a still coupled cardiovascular system with preserved CO reserve, no hemodynamic signs of pulmonary vascular remodeling, and without overt right heart involvement. Thus, this cluster of patients would perfectly qualify for pharmacological treatment implementation and for device treatment, including transcatheter LA shunting and, potentially, splanchnic denervation [34].

Clusters 4 and 5 presented the more advanced hemodynamic phenotype, despite diuretic treatment. Tall V waves in the PAWP position, consistent with a stiff LA, were present already at rest in Cluster 4, together with a precapillary component to PH, as well as RA hypertension. Additionally, during exercise, CO reserve was reduced, and signs of hemodynamically-relevant TR and/or RA myopathy [17] could be observed. Cluster 5 had low CO and signs of hemodynamically-relevant TR and/or RA myopathy [17] already evident at rest, and developed a precapillary component to PH during exercise. The absence of tall V waves in the PAWP position, both at rest and during exercise, despite LA enlargement and a high prevalence of atrial fibrillation, could be speculatively attributed to LV underfilling in the presence of severe TR and low CO [14], or to pulmonary vascular remodeling attenuating pressure transmission from the LA. These two more advanced hemodynamic clusters, which were numerically less represented, could not be candidate to LA shunting, while they might potentially benefit from splanchnic denervation as well as from interventions on the tricuspid valve [35, 36]. Additionally, innovative medical treatments, such as oral levosimendan [37], may appear particularly appealing in this situation.



CENTRAL ILLUSTRATION | Five clusters of HFpEF patients were obtained by applying unsupervised cluster analysis to eight non-highly correlated hemodynamic variables collected at rest, during passive leg raise, and at peak exercise right heart catheterization. These five clusters represent different stages in HFpEF progression, from left ventricular diastolic dysfunction to left atrial failure, pulmonary vascular and right heart involvement, with prognostic implications. Abbreviations: CO, cardiac output; CpcPH, combined post- and precapillary pulmonary hypertension; HFpEF, heart failure with preserved ejection fraction; LA, left atrium; LAH, left atrial hypertension; NTproBNP, N-terminal pro brain natriuretic peptide; PAP, pulmonary artery pressure; PH, pulmonary hypertension; PVD, pulmonary vascular disease; RA, right atrium; RAH, right atrial hypertension; RHC, right heart catheterization; TR, tricuspid regurgitation.

4.2 | Study Limitations

This was a relatively small, single-center study, with a high likelihood of selection bias. Accordingly, some clusters were relatively underrepresented, although relative underrepresentation of more severe phenotypes is not uncommon in this kind of HFpEF cohorts undergoing exercise hemodynamic evaluation. We sought to compensate the relatively small sample size by careful waveform analysis, providing additional information over those normally highlighted in clinical practice, that may nonetheless bear pathophysiological meaning. Additionally, we did not externally validate the results obtained in our cohort. Sodium-glucose cotransporter-2 inhibitors were not approved in Italy for the treatment of HFpEF during the study period. Accordingly, no patient received such drugs. Obesity, defined by body mass index > 30 Kg/m^2, was relatively underrepresented in our study (25% of the cohort). We had previously discussed that our Italian population may be mainly an older, nonobese female cohort [11], which differs from other studies on exercise hemodynamics in HFpEF [2–7], likely reflecting the different, albeit rising, burden of obesity around the globe. Additionally, we could not provide other indices of adiposity. To make a comparison, in a recent analysis from the PVDOMICS study [38], of 276 patients with HFpEF, 89% had increased waist/height ratio and 60% had body mass index > 30 Kg/m^2, highlighting the limits of body mass index alone in detecting adiposity. In that study, indices of adiposity were clearly associated with hemodynamic abnormalities (PAWP at rest and during exercise) and with exercise limitation. However, the association between excess adiposity and RA pressure was less evident [38], albeit having already been highlighted in other reports [39]. Additionally, despite the strong association between adiposity and hemodynamic abnormalities, some of these latter (i.e., LA myopathy) may still progress despite bariatric surgery in obese HFpEF [40]. Finally, body mass index has not been associated with deterioration of RV structure and function over time in HFpEF [7].

5 | Conclusion

Unsupervised cluster analysis of a comprehensive "dynamic" hemodynamic evaluation, adopting provocative tests in the cath lab, provided a data-driven classification of HFpEF patients. Five clusters of HFpEF patients were identified, reflecting distinct pathophysiological stages of the disease, with progressive LV diastolic dysfunction, LA myopathy, pulmonary vascular and right heart involvement, portending poor prognosis. Further analysis is needed to confirm that this advanced hemodynamic phenotyping may aid in risk stratification and in guiding individualized treatment approaches.

Short Tweet

Unsupervised cluster analysis of advanced hemodynamics subdivides HFpEF in different stages of disease progression,

from LV diastolic dysfunction, to LA failure, pulmonary vascular and right heart involvement, with prognostic implications. #HeartFailure #Peoplesventricle.

Author Contributions

Sergio Caravita is the guarantor of the manuscript and takes responsibility for the integrity of the work as a whole. Sergio Caravita and Claudia Baratto conceived and designed the study. Data collection was performed by Sergio Caravita and Claudia Baratto. Data analysis and interpretation were conducted by Ettore Lanzarone, Sergio Caravita, and Claudia Baratto. The manuscript was drafted by Sergio Caravita, Claudia Baratto, Céline Dewachter, Veraprapas Kittipibul, Giovanni Battista Perego, Fabio Previdi, Stefano Paleari, Mattia Cattaneo, Luigi P. Badano, Michele Senni, Marat Fudim, Gianfranco Parati, and Jean-LucVachiéry critically revised the manuscript for important intellectual content. Statistical analysis was performed by Ettore Lanzarone. Overall supervision of the study was provided by Giovanni Battista Perego, FabioPrevidi, Stefano Paleari, Mattia Cattaneo, Luigi P. Badano, Michele Senni, Marat Fudim, Gianfranco Parati, and Jean-LucVachiéry. All authors have read and approved the final version of the manuscript and take responsibility for all aspects of the work.

Acknowledgments

The authors would like to express their gratitude to the nurses of the cath lab, Ospedale San Luca IRCCS Istituto Auxologico Italiano, for their invaluable support in performing exercise hemodynamic tests, including Francesca Boniolo, Pierpaolo Di Pierro, Giuseppe Di Stasio, Marta Maria Fasano, Andrea Fiorentini, Annalisa Friggi, Cesare Longo, Jana Quario Rondo, and Marco Setti. The authors are grateful to Laboratori Guidotti S.p.A. for providing free-of-charge software for echocardiographic analysis. This work was funded by the National Plan for NRRP Complementary Investments (PNC, established with the decree-law 6 May 2021, n. 59, converted by law n. 101 of 2021) in the call for the funding of research initiatives for technologies and innovative trajectories in the health and care sectors (Directorial Decree n. 931 of 06-06-2022)—project n. PNC0000003—AdvaNced Technologies for Human-centrEd Medicine (project acronym: ANTHEM). This work reflects only the authors' views and opinions; neither the Ministry for University and Research nor the European Commission can be considered responsible for them. Open access publishing facilitated by Universita degli Studi di Bergamo, as part of the Wiley - CRUI-CARE agreement.

Ethics Statement

This study was approved by the local Ethics Committee (protocol n 2022_09_27_01 approved on September 27, 2022). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Conflicts of Interest

Dr. Fudim was supported by the NIH, Sardocor, and Doris Duke. He is a consultant/has ownership interesting in Abbott, Ajax, Alio Health, Alleviant, Analog, Andera, Artha, Audicor, AxonTherapies, Bayer, Bodyguide, Bodyport, Boston Scientific, Broadview, Cadence, Cardioflow, Coridea, CVRx, Daxor, Edwards LifeSciences, Echosens, EKO, Feldschuh Foundation, Fire1, FutureCardia, Galvani, Gradient, Hatteras, HemodynamiQ, Impulse Dynamics, Intershunt, Medtronic, Merck, NIMedical, NovoNordisk, NucleusRx, NXT Biomedical, Orchestra, Pharmacosmos, Presidio, Procyreon, Proton Intelligence, ReCor, SCPharma, Shifamed, Splendo, Lumina, Summacor, SyMap, Verily, Vironix, Viscardia, and Zoll. Dr. Caravita reports consultancy fees from Alleviant, MSD, Janssen, and Tenax Therapeutics. Dr. Senni reports consultancy fees from Novartis, Merck, Vifor Pharma, Abbott, Boehringer Ingelheim, Bioventrix, Servier, and Novo Nordisk. Dr. Vachiéry is a consultant to Merck. The remaining authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
e-Figure 1: Within cluster sum of squares (WCSS) as a function of the number clusters. **e-table 1:** Pearson correlation coefficients between hemodynamic variables.