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

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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; H₂FPEF, 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; VO₂, oxygen consumption.

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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 H₂FPEF (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 7F 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 $(\text{mean PA pressure} - \text{mean PAWP})/\text{CO}$.

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/m² 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/VO₂ 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/VO₂ 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/m² 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 ≥ 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.

| Clinical Features | Cluster 1 | | Cluster 2 | | Cluster 3 | | Cluster 4 | | Cluster 5 | |
|-----------------------|------------------------|--------------------|---------------------|------------------------------|------------------------|------------------------------|------------------------------|------------------------------|---------------------|-----------------|
| | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females |
| Sex | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females | Female predominance | Males = females |
| Rhythm | Sinus rhythm | Sinus rhythm | Sinus rhythm | Sinus rhythm/paroxysmal AFib | Sinus rhythm | Sinus rhythm/paroxysmal AFib | Sinus rhythm/paroxysmal AFib | Sinus rhythm/paroxysmal AFib | Sinus rhythm | AfFib |
| NTproBNP | Low | Intermediate-low | Intermediate-low | Intermediate-high | Intermediate-low | Intermediate-high | Intermediate-high | High | High | High |
| HFpEF scores | Low | Intermediate | Intermediate | High | Low | High | High | High | High | High |
| Left atrium | Steep LA pressure rise | Exercise LAH | Exercise LAH | LAH | Steep LA pressure rise | Exercise LAH | Exercise LAH | LAH | LAH | LAH |
| Hemodynamics | Non-stiff LA | Non-stiff LA | Non-stiff LA | Latent stiff LA | Non-stiff LA | Latent stiff LA | Latent stiff LA | Shiff LA | LA underfilling | LA underfilling |
| Pulmonary circulation | No PH | Exercise PH | Exercise PH | PH | No PH | Exercise PH | PH | PH | PH | PH |
| | Normal CO | Normal CO | Normal CO | Normal CO | Normal CO | Normal CO | Normal CO | Low CO reserve | Low CO | Low CO |
| | Normal PVR | Normal PVR | Normal PVR | Normal PVR | Normal PVR | Normal PVR | Normal PVR | CpcPH | Latent PVD | Latent PVD |
| | No RAH | Exercise RAH | Exercise RAH | Exercise RAH | Exercise RAH | Exercise RAH | Exercise RAH | RAH | RAH | RAH |
| Right Atrium | Non-stiff RA/no TR | Non-stiff RA/no TR | Non-stiff RA/no TR | Non-stiff RA/no TR | Non-stiff RA/no TR | Non-stiff RA/no TR | Non-stiff RA/no TR | Latent RA myopathy/TR | 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 \geq 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: cardio-metabolic (body mass index $> 30 \text{ Kg/m}^2$ or diabetes mellitus), LA myopathy (LA volume index $> 34 \text{ mL/m}^2$ or any history of atrial fibrillation), PVD (mean PA pressure $> 20 \text{ mmHg}$ and PVR $> 2 \text{ WU}$), and vascular stiffening (pulse pressure $> 90 \text{ mmHg}$ or total arterial compliance index $< 0.5 \text{ mL/m}^2/\text{mmHg}$). 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 ₂ FPEF 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; H₂FPEF, 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 regurgitation; 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

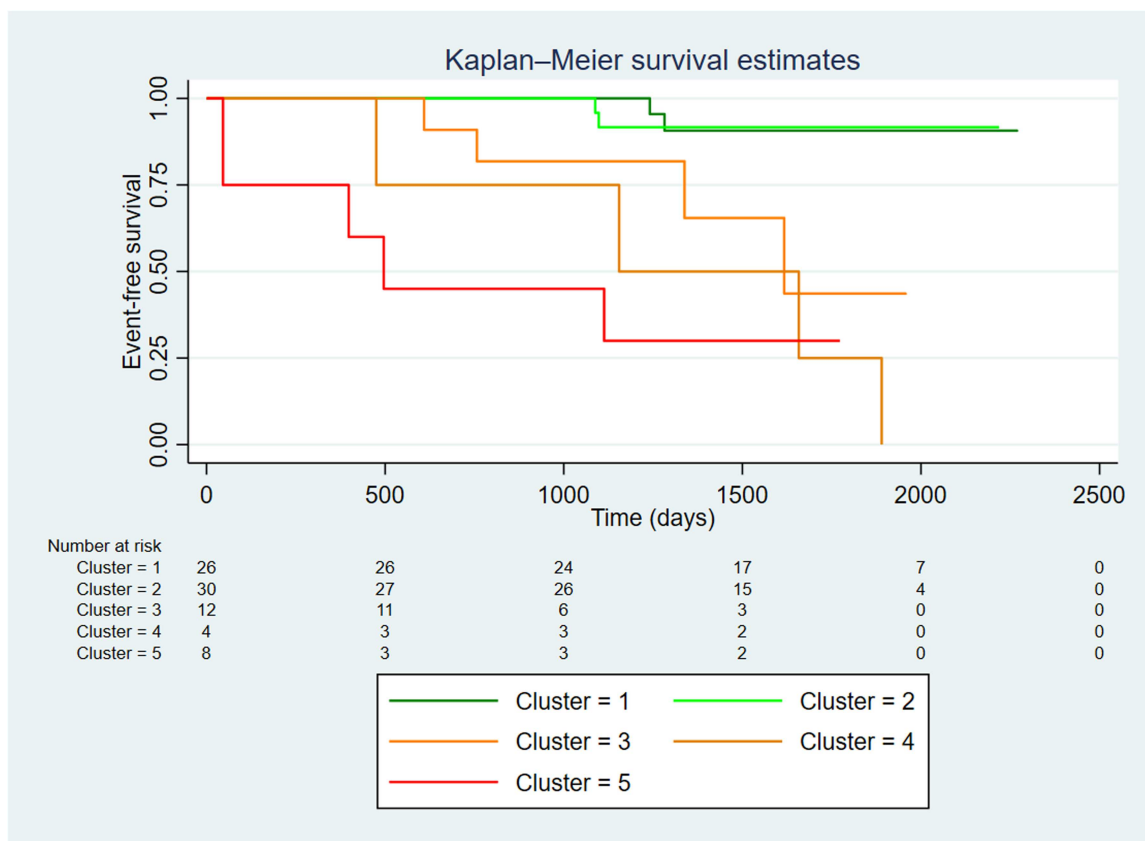


FIGURE 1 | Kaplan-Meier curves for event-free survival in the five clusters of patients.

HFpEF (low or intermediate H₂FPEF 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.

**N=80 HFpEF
with rest+exercise RHC**

Unsupervised cluster analysis with non-highly correlated hemodynamic data

| PAWP | PAWP V wave amplitude | PAWP/CO slope | mPAP/CO slope | Pulmonary Vascular Resistance (PVR) | Cardiac Index | CO/VO ₂ slope | RA pressure systolic amplitude |
|------------------|-----------------------|---------------|--|-------------------------------------|---------------|--|--------------------------------|
| Left atrium (LA) | | | Pulmonary blood flow and vascular resistance | | | Right atrium (RA) & tricuspid regurgitation (TR) | |

Interpretation and integration with clinical data

| | | 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 |
| | | Non-stiff LA | Non-stiff LA | Latent LA myopathy | LA myopathy | LA underfilling |
| | PULMONARY CIRCULATION | 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 |

Transition from «left heart» to «right heart» phenotype & ↑disease severity

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/m², 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/m², 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, Verapras Kittipibul, Giovanni Battista Perego, Fabio Previdi, Stefano Paleari, Mattia Cattaneo, Luigi P. Badano, Michele Senni, Marat Fudim, Gianfranco Parati, and Jean-Luc Vachiéry 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, Fabio Previdi, Stefano Paleari, Mattia Cattaneo, Luigi P. Badano, Michele Senni, Marat Fudim, Gianfranco Parati, and Jean-Luc Vachiéry. All authors have read and approved the final version of the manuscript and take responsibility for all aspects of the work.

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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 interest 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.

References

1. C. Baratto, S. Caravita, D. Soranna, et al., "Exercise Haemodynamics in Heart Failure With Preserved Ejection Fraction: A Systematic Review and Meta-Analysis," *ESC Heart Failure* 9, no. 5 (2022): 3079–3091, <https://doi.org/10.1002/ehf2.13979>.
2. B. A. Borlaug, R. A. Nishimura, P. Sorajja, C. S. P. Lam, and M. M. Redfield, "Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction," *Circulation: Heart Failure* 3, no. 5 (2010): 588–595, <https://doi.org/10.1161/CIRCHEARTFAILURE.109.930701>.
3. J. E. Ho, E. K. Zern, L. Wooster, et al., "Differential Clinical Profiles, Exercise Responses, and Outcomes Associated With Existing HFpEF Definitions," *Circulation* 140, no. 5 (2019): 353–365, <https://doi.org/10.1161/CIRCULATIONAHA.118.039136>.
4. D. Popovic, A. Alogna, M. Omar, et al., "Ventricular Stiffening and Chamber Contracture in Heart Failure With Higher Ejection Fraction," *European Journal of Heart Failure* 25, no. 5 (2023): 657–668, <https://doi.org/10.1002/ejhf.2843>.
5. M. Tamargo, M. Obokata, Y. N. V. Reddy, et al., "Functional Mitral Regurgitation and Left Atrial Myopathy in Heart Failure With Preserved Ejection Fraction," *European Journal of Heart Failure* 22, no. 3 (2020): 489–498, <https://doi.org/10.1002/ejhf.1699>.
6. Y. N. V. Reddy, M. Obokata, F. H. Verbrugge, G. Lin, and B. A. Borlaug, "Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation," *Journal of the American College of Cardiology* 76, no. 9 (2020): 1051–1064, <https://doi.org/10.1016/j.jacc.2020.07.009>.
7. M. Obokata, Y. N. V. Reddy, V. Melenovsky, S. Pislaru, and B. A. Borlaug, "Deterioration in Right Ventricular Structure and Function Over Time in Patients With Heart Failure and Preserved Ejection Fraction," *European Heart Journal* 40, no. 8 (2019): 689–697, <https://doi.org/10.1093/eurheartj/ehy809>.
8. C. Baratto, S. Caravita, C. Dewachter, et al., "Right Heart Adaptation to Exercise in Pulmonary Hypertension: An Invasive Hemodynamic Study," *Journal of Cardiac Failure* 29, no. 9 (2023): 1261–1272, <https://doi.org/10.1016/j.cardfail.2023.04.009>.
9. C. Baratto, C. Dewachter, K. Forton, et al., "Right Ventricular Reserve in Cardiopulmonary Disease: A Simultaneous Hemodynamic and Three-Dimensional Echocardiographic Study," *Journal of Heart and Lung Transplantation* 44, no. 6 (2025): 916–926, <https://doi.org/10.1016/j.healun.2024.12.022>.
10. S. Caravita, C. Baratto, A. Filippo, et al., "Shedding Light on Latent Pulmonary Vascular Disease in Heart Failure With Preserved Ejection Fraction," *JACC: Heart Failure* 11, no. 10 (2023): 1427–1438, <https://doi.org/10.1016/j.jchf.2023.03.003>.
11. C. Baratto, S. Caravita, D. Soranna, et al., "Current Limitations of Invasive Exercise Hemodynamics for the Diagnosis of Heart Failure With Preserved Ejection Fraction," *Circulation: Heart Failure* 14, no. 5 (2021): e007555, <https://doi.org/10.1161/CIRCHEARTFAILURE.120.007555>.
12. C. Baratto, A. Faini, G. P. Gallone, et al., "Pulmonary Artery Wedge Pressure and Left Ventricular End-Diastolic Pressure During Exercise in Patients With Dyspnoea," *ERJ Open Research* 9, no. 4 (2023): 00750–2022, <https://doi.org/10.1183/23120541.00750-2022>.
13. E. Lanzarone, C. Baratto, M. Vicenzi, et al., "Haemodynamic Validation of the Three-Step HFA-PEFF Algorithm to Diagnose Heart Failure With Preserved Ejection Fraction," *ESC Heart Failure* 10, no. 4 (2023): 2588–2595, <https://doi.org/10.1002/ehf2.14436>.
14. C. Baratto, S. Caravita, G. Corbetta, et al., "Impact of Severe Secondary Tricuspid Regurgitation on Rest and Exercise Hemodynamics of

- Patients With Heart Failure and a Preserved Left Ventricular Ejection Fraction,” *Frontiers in Cardiovascular Medicine* 10 (2023): 1061118, <https://doi.org/10.3389/fcvm.2023.1061118>.
15. Y. N. V. Reddy, R. E. Carter, M. Obokata, M. M. Redfield, and B. A. Borlaug, “A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction,” *Circulation* 138, no. 9 (2018): 861–870, <https://doi.org/10.1161/CIRCULATIONAHA.118.034646>.
16. B. Pieske, C. Tschöpe, R. A. Boer, de, et al., “How to Diagnose Heart Failure With Preserved Ejection Fraction: The HFA–PEFF Diagnostic Algorithm: A Consensus Recommendation From the Heart Failure Association (HFA) of the European Society of Cardiology (ESC),” *European Heart Journal* 40, no. 40 (2019): 3297–3317, <https://doi.org/10.1093/eurheartj/ehz641>.
17. S. Caravita, M. Liberatore, L. P. Badano, et al., “Determinants of Right Heart Hemodynamic Derangement in Patients With and Without Tricuspid Regurgitation,” *Circulation: Heart Failure* 18, no. 8 (2025): e012813, <https://doi.org/10.1161/CIRCHEARTFAILURE.125.012813>.
18. S. E. Litwin, J. Komtebedde, M. Hu, et al., “Exercise-Induced Left Atrial Hypertension in Heart Failure With Preserved Ejection Fraction,” *JACC: Heart Failure* 11, no. 8 Pt 2 (2023): 1103–1117, <https://doi.org/10.1016/j.jchf.2023.01.030>.
19. M. Humbert, G. Kovacs, M. M. Hoeper, et al., “2022 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension,” *European Heart Journal* 43, no. 38 (2022): 3618–3731, <https://doi.org/10.1093/eurheartj/ehac237>.
20. B. A. Borlaug, J. Blair, M. W. Bergmann, et al., “Latent Pulmonary Vascular Disease May Alter the Response to Therapeutic Atrial Shunt Device in Heart Failure,” *Circulation* 145, no. 21 (2022): 1592–1604, <https://doi.org/10.1161/CIRCULATIONAHA.122.059486>.
21. M. K. Mahowald, R. A. Nishimura, S. V. Pislaru, et al., “Reduction in Right Atrial Pressures Is Associated With Hemodynamic Improvements After Transcatheter Edge-To-Edge Repair of the Tricuspid Valve,” *Circulation: Cardiovascular Interventions* 14, no. 12 (2021): e010557, <https://doi.org/10.1161/CIRCINTERVENTIONS.121.010557>.
22. M. Senni, S. Caravita, and W. J. Paulus, “Do Existing Definitions Identify Subgroup Phenotypes or Reflect the Natural History of Heart Failure With Preserved Ejection Fraction?,” *Circulation* 140, no. 5 (2019): 366–369, <https://doi.org/10.1161/CIRCULATIONAHA.119.041657>.
23. C. Baratto, S. Caravita, and J. L. Vachiéry, “Pulmonary Hypertension Associated With Left Heart Disease,” *Seminars in Respiratory and Critical Care Medicine* 44, no. 6 (2023): 810–825, <https://doi.org/10.1055/s-0043-1772754>.
24. A. Uijl, G. Savarese, I. Vaartjes, et al., “Identification of Distinct Phenotypic Clusters in Heart Failure With Preserved Ejection Fraction,” *European Journal of Heart Failure* 23, no. 6 (2021): 973–982, <https://doi.org/10.1002/ehf.2169>.
25. K. Larson, M. Omar, H. Sorimachi, et al., “Clinical Phenogroup Diversity and Multiplicity: Impact on Mechanisms of Exercise Intolerance in Heart Failure With Preserved Ejection Fraction,” *European Journal of Heart Failure* 26, no. 3 (2024): 564–577, <https://doi.org/10.1002/ehf.3105>.
26. A. M. Janowski, K. S. Ravellette, M. Insel, J. G. N. Garcia, F. P. Rischard, and R. R. Vanderpool, “Advanced Hemodynamic and Cluster Analysis for Identifying Novel RV Function Subphenotypes in Patients With Pulmonary Hypertension,” *Journal of Heart and Lung Transplantation* 43, no. 5 (2024): 755–770, <https://doi.org/10.1016/j.healun.2023.12.009>.
27. S. Caravita, C. Baratto, and M. Fudim, “Why Do Exercise Hemodynamics Matter?,” *Journal of Cardiac Failure* 29, no. 9 (2023): 1285–1287, <https://doi.org/10.1016/j.cardfail.2023.05.002>.
28. H. M. Salah, C. Baratto, D. M. Yaranov, et al., “Interatrial Shunt Devices,” *Heart failure clinics* 20, no. 1 (2024): 61–69, <https://doi.org/10.1016/j.hfc.2023.05.003>.
29. D. R. Florescu, D. Muraru, C. Florescu, et al., “Right Heart Chambers Geometry and Function in Patients With the Atrial and the Ventricular Phenotypes of Functional Tricuspid Regurgitation,” *European Heart Journal—Cardiovascular Imaging* 23, no. 7 (2022): 930–940, <https://doi.org/10.1093/ehjci/jeab211>.
30. D. R. Florescu, D. Muraru, V. Volpato, et al., “Atrial Functional Tricuspid Regurgitation as a Distinct Pathophysiological and Clinical Entity: No Idiopathic Tricuspid Regurgitation Anymore,” *Journal of Clinical Medicine* 11, no. 2 (2022): 382, <https://doi.org/10.3390/jcm11020382>.
31. D. Muraru, S. Caravita, A. C. Guta, et al., “Functional Tricuspid Regurgitation and Atrial Fibrillation: Which Comes First, the Chicken or the Egg?,” *CASE 4*, no. 5 (2020): 458–463, <https://doi.org/10.1016/j.case.2020.04.011>.
32. M. Fudim, D. M. Kaye, B. A. Borlaug, et al., “Venous Tone and Stressed Blood Volume in Heart Failure: JACC Review Topic of the Week,” *Journal of the American College of Cardiology* 79, no. 18 (2022): 1858–1869, <https://doi.org/10.1016/j.jacc.2022.02.050>.
33. Y. N. V. Reddy, A. El-Sabbagh, and R. A. Nishimura, “Comparing Pulmonary Arterial Wedge Pressure and Left Ventricular End-Diastolic Pressure for Assessment of Left-Sided Filling Pressures,” *JAMA Cardiology* 3, no. 6 (2018): 453–454, <https://doi.org/10.1001/jamacardio.2018.0318>.
34. M. Fudim, M. S. Khan, A. A. Paracha, K. Sunagawa, and D. Burkhoff, “Targeting Preload in Heart Failure: Splanchnic Nerve Blockade and Beyond,” *Circulation: Heart Failure* 15, no. 3 (2022): e009340, <https://doi.org/10.1161/CIRCHEARTFAILURE.121.009340>.
35. R. T. Hahn, J. Lindenfeld, M. Böhm, et al., “Tricuspid Regurgitation in Patients With Heart Failure and Preserved Ejection Fraction: JACC State-of-the-Art Review,” *Journal of the American College of Cardiology* 84, no. 2 (2024): 195–212, <https://doi.org/10.1016/j.jacc.2024.04.047>.
36. V. N. Rao, E. Kozaily, and R. J. Tedford, “Letting Go of Restraint: Tricuspid Valve Intervention in Heart Failure With Preserved Ejection Fraction,” *European Journal of Heart Failure* 26, no. 4 (2024): 1036–1038, <https://doi.org/10.1002/ehf.3254>.
37. H. Yaku, D. Burkhoff, B. A. Borlaug, et al., “Oral Levosimendan for the Treatment of Pulmonary Hypertension Due to Heart Failure With Preserved Ejection Fraction: Rationale and Design of the LEVEL Trial,” *Journal of Cardiac Failure* S1071-9164, no. 25 (2025): 00293-3, <https://doi.org/10.1016/j.cardfail.2025.06.009>.
38. Y. N. V. Reddy, R. P. Frantz, A. R. Hemnes, et al., “Disentangling the Impact of Adiposity From Insulin Resistance in Heart Failure With Preserved Ejection Fraction,” *Journal of the American College of Cardiology* 85, no. 18 (2025): 1774–1788, <https://doi.org/10.1016/j.jacc.2025.03.530>.
39. H. Sorimachi, K. Omote, M. Omar, et al., “Sex and Central Obesity in Heart Failure With Preserved Ejection Fraction,” *European Journal of Heart Failure* 24, no. 8 (2022): 1359–1370, <https://doi.org/10.1002/ehf.2563>.
40. H. Sorimachi, M. Obokata, K. Omote, et al., “Long-Term Changes in Cardiac Structure and Function Following Bariatric Surgery,” *Journal of the American College of Cardiology* 80, no. 16 (2022): 1501–1512, <https://doi.org/10.1016/j.jacc.2022.08.738>.

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.