Implications of peripheral oedema in heart failure with preserved ejection fraction: a heart failure network analysis

Marat Fudim1*, Nicolas Ashur1, Aaron D. Jones2, Andrew P. Ambrosy3, Bradley A. Bart4, Javed Butler5, Horng H. Chen6, Stephen J. Greene1, Yogesh Reddy6, Margaret M. Redfield6, Abhinav Sharma7, Adrian F. Hernandez1,2, Gary Michael Felker1,2, Barry A. Borlaug6 and Robert J. Mentz1,2

1Department of Medicine, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27713, USA; 2Duke Clinical Research Institute, Durham, NC, USA; 3Kaiser Permanente, San Francisco, CA, USA; 4Minneapolis VA Medical Center, Minneapolis, MN, USA; 5Department of Medicine, University of Mississippi, Jackson, MS, USA; 6Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; 7Division of Cardiology, McGill University Health Centre, McGill University, Montreal, Quebec, Canada

Abstract

Aims Heart failure with preserved ejection fraction (HfPfEF) is a heterogeneous condition, and tissue congestion manifested by oedema is not present in all patients. We compared clinical characteristics, exercise capacity, and outcomes in patients with HfPfEF with and without oedema.

Methods and results This study was a post hoc analysis of pooled data of patients with left ventricular ejection fraction of ≥50% enrolled in the DOSE, CARRESS-HF, RELAX, ATHENA, ROSE, INDIE, and NEAT trials. Patients were dichotomized by the severity of oedema. Cox proportional hazard regression and generalized linear regression models were used to assess associations between oedema, symptoms, and clinical outcomes. The ambulatory cohort included 393 patients (228 with and 165 without oedema), and the hospitalized cohort included 338 patients (249 with moderate oedema and 89 with mild or none). Among ambulatory patients, patients with oedema had a higher body mass index (35.2 kg/m² [inter-quartile range, IQR 30.5, 41.6] vs. 31.6 kg/m² [IQR 27.9, 36.3], \( P < 0.001 \)), greater burden of co-morbidities, higher intravascular pressures estimated on physical examination (elevated jugular venous pressure: 50% vs. 24.7%, \( P < 0.001 \)), poorer renal function (creatinine: 1.2 mg/dL [IQR 0.9, 1.5] vs. 1 mg/dL [IQR 0.8, 1.3], \( P = 0.003 \)), and lower peak \( VO_2 \) (adjusted mean difference \(-1.04 \text{ mL/kg/min}, 95\% \text{ confidence interval} [-1.71, -0.37], P < 0.003 \)). Among hospitalized patients, despite greater in-hospital fluid/weight loss in the moderate oedema group, there was no difference in the improvement in dyspnoea by the visual analogue scale or well-being visual analogue scale from baseline to 3–4 days and no statistically significant difference in the rate of 60 day rehospitalization/death (adjusted hazard ratio 1.44, 95% confidence interval [0.87, 2.39], \( P = 0.156 \)).

Conclusions Patients with HfPfEF and oedema display higher body mass, greater burden of co-morbidities, and more severe exercise intolerance, but clinical responses to treatment appear similar. Further research is required to better understand the nature of volume distribution in different HfPfEF phenotypes.

Keywords Heart failure; Congestion; Oedema

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*Correspondence to: Marat Fudim, Department of Medicine, Duke University Medical Center, 2301 Erwin Road, Durham, NC 27713, USA. Tel: 917-544-4377. Email: marat.fudim@duke.edu

Introduction

Vascular and tissue congestion are hallmarks of decompen-sated heart failure (HF). However, the concept of volume retention as the principal cause of acute or chronic HF decompensation has recently been challenged.1–3 An alternate hypothesis suggests that volume redistribution, via decreased vascular capacitance and intercompartmental fluid shifts, is an important contributor to cardiopulmonary congestion. Patients with this pathophysiology may not display...
true plasma volume expansion but rather suffer from acute episodes of volume redistribution resulting in higher filling pressures. Oedema may be absent in such patients. Patients with HF with preserved ejection fraction (HFrEF) are particularly fluid sensitive and prone to cardiac decompensation. Broadly, two extreme clinical volume phenotypes of HFrEF may exist: (i) extravascular fluid overload as the driver of clinical symptoms (e.g. peripheral oedema, weight gain, and abdominal distention) and (ii) dyspnoea on exertion without objective findings of fluid retention (volume redistribution phenotype). Volume status as assessed on physical exam is a surrogate of intravascular and total body volume and may differentiate the two volume phenotypes outlined earlier. While the proposed physiology of volume distribution is very likely not black and white/ond–off, we aimed to assess the clinical profile and functional outcomes of these ostensible HFrEF ‘volume phenotypes’ based upon the presence or absence of peripheral oedema, utilizing a large pooled cohort of well-characterized patients including those in the ambulatory setting. We also explored whether the same concept holds true for patients who were hospitalized for acute HFrEF.

**Methods**

This post hoc analysis was performed using pooled data from the National Heart, Lung, and Blood Institute-sponsored Heart Failure Network DOSE (Diuretic Optimization Strategies Evaluation), CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure), RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction), ATHENA (Al-dosterone Targeted Neurohormonal Combined With Natriuresis Therapy—HF), ROSE (Renal Optimization Strategies Evaluation), INDIE (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure With Preserved Ejection Fraction), and NEAT (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trials. Common and rigorous entry criteria were required to verify the diagnosis of HFrEF in the trials, specifically New York Heart Association Class II–IV HF symptoms, left ventricular ejection fraction ≥50%, and objective evidence of HF based upon prior hospitalization, invasive haemodynamics, elevated natriuretic peptide levels, or echocardiographic diastolic dysfunction together with chronic use of a loop diuretic. Participants in RELAX and INDIE were additionally required to have peak oxygen consumption (peak VO2) with cardiopulmonary exercise of ≤60% and ≤75% predicted, respectively, with peak respiratory exchange ratio ≥1.0. Detailed inclusion and exclusion criteria from these trials are included in Supporting Information, Tables S1 and S2. Each protocol was approved by the institutional review boards at each site, and written informed consent was obtained from all patients prior to randomization.

**Ambulatory cohort**

The ambulatory cohort included patients from the INDIE, NEAT, and RELAX trials. Oedema was defined using common clinical scales (Supporting Information, Table S3). Patients were divided into (i) no oedema and (ii) oedema at baseline (included trace, mild, moderate, and severe). We evaluated a change in exercise function from baseline to 12 weeks such as peak VO2 (NEAT excluded because it did not perform cardiopulmonary exercise testing) and 6 min walking from baseline to 12 weeks (INDIE excluded).

**Hospitalized cohort**

In an exploratory analysis, we extended the concept of volume phenotypes using peripheral oedema as a surrogate to the hospitalized patients with HFrEF from the ATHENA, CARRESS, DOSE, and ROSE trials. The trial cohorts were pooled and divided based on peripheral oedema status upon randomization. Oedema grades were investigator reported as (Supporting Information, Table S3) (i) ‘no to mild’ and (ii) ‘moderate to severe’ oedema. We evaluated the change in physical exam [clinical decongestion, defined as jugular venous pressure [JVP] <8 cm, no orthopnoea, and ≤mild oedema] and patient-reported measures of decongestion [dyspnoea and global well-being visual analogue scale (VAS)] from baseline to 3–4 days and 7 days/discharge. Additional measures included the change in glomerular filtration rate and net fluid removal from baseline to 3–4 and at 7 days/discharge. Finally, we evaluated all-cause rehospitalization/death at 30 and 60 days (the ATHENA trial had follow-up through 30 days).

The higher prevalence of oedema in the hospitalized cohort explains the different definitions used for oedema comparison groups in the hospitalized vs. ambulatory cohorts. To allow comparison between oedema groups within pooled, heterogeneous trials, the baseline characteristics were adjusted for age, sex, race, and clinical trial. Categorical variables were presented as counts, and differences between the two groups were assessed using logistic regression with and without adjustment. Continuous variables were presented as medians, and the differences between high-volume and low-volume groups were assessed using linear regression with and without adjustment. Multivariable Cox proportional hazard regression models were used to assess the association between oedema and time to rehospitalization or death, and multivariable generalized linear regression models were used for the remainder of the
outcome analyses. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC), and two-tailed $P < 0.05$ was considered statistically significant.

## Results

The ambulatory cohort included 393 patients, of whom 228 (58%) had oedema and 165 (42%) had no oedema. The distribution of oedema grades is presented in Supporting Information, Table S4. At baseline, patients with peripheral oedema tended to be older (69 years [inter-quartile range, IQR 63, 76] vs. 67 years [IQR 59, 75], $P = 0.009$), more likely to have diabetes (44.3% vs. 32.7%, $P = 0.015$), with a higher median creatinine (1.2 mg/dL [IQR 0.9, 1.5] vs. 1 mg/dL [IQR 0.8, 1.3], $P = 0.003$), body mass index (35.2 kg/m$^2$ [IQR 30.5, 41.6] vs. 31.6 kg/m$^2$ [IQR 27.9, 36.3], $P < 0.001$), and elevated JVP (50% vs. 24.7%, $P < 0.001$). Ambulatory patients with oedema had a higher use of calcium channel blockers (oedema: 36.4% vs. no oedema: 24.2%). Patients with oedema had higher right ventricular systolic pressure when compared with no oedema. There were no other significant differences in echocardiographic parameters. The prevalence of prior HF hospitalization was similar between those with and without oedema (Table 1). Follow-up oedema status was not available in RELAX, but in INDIE and NEAT, about one-fourth of each baseline oedema group shifted to the other group after 12 weeks. Of those with no oedema at baseline, 22/76 (28.9%) had ≥trace oedema at 12 weeks. Of those with ≥trace oedema at baseline, 26/103 (25.2%) had no oedema at 12 weeks.

In the ambulatory cohort, presence of oedema was associated with a similar median peak VO$_2$ at baseline (no oedema: 1247 ml/min [IQR 885, 1619] vs. 1158 ml/min [IQR 977, 1480], $P = 0.315$). When averaged by weight, patients with oedema at baseline had lower median peak VO$_2$ at baseline when averaged by weight (12 ml/kg/min [IQR 10, 14] vs. 14 ml/kg/min [IQR 11, 16], $P = 0.002$) but no significant difference in the change in peak VO$_2$ at 12 weeks (adjusted mean difference $-0.22$ ml/kg/min, 95% confidence interval, CI $[-0.70, 0.26]$, $P = 0.37$). The adjusted 6 min walk distance between groups was not significantly different at baseline or at 12 week follow-up (all $P > 0.05$).

The hospitalized cohort included 338 patients, of whom 249 (74%) had at least moderate oedema. Patients with at least moderate oedema had higher body mass index (34.5 kg/m$^2$ [IQR 28.1, 42.2] vs. 30.9 kg/m$^2$ [IQR 26.8, 36.8], $P < 0.001$) and more likely to have JVP of at least 13 cm H$_2$O (75.8% vs. 48%, $P < 0.001$) than patients with none or mild oedema. Both volume phenotypes had a comparable co-morbidity burden and median N-terminal prohormone of brain natriuretic peptide (3332 pg/mL [IQR 1757, 6336] vs. 2945 pg/mL [IQR 1538–5906], $P = 0.512$) (Table 2).

At baseline, patients with a greater degree of peripheral oedema experienced a similar degree of dyspnoea but lower levels of global well-being (43 [IQR 25–62] vs. 52 [IQR 34–69], $P = 0.033$).

During follow-up, patients in the hospitalized cohort with at least moderate oedema experienced greater weight loss ($-8$ lb, 95% CI $[-13, -4]$ vs. $-4$ lb, 95% CI $[-8, -1]$), adjusted $P = 0.012$) from baseline to 3–4 days and net fluid loss (adjusted mean difference from baseline to 3–4 days, $-1356$ ml, 95% CI $[-535, -2178]$, $P = 0.001$), but a lower likelihood of clinical decongestion (JVP < 8 cm H$_2$O, no orthopnoea, and peripheral oedema < moderate) at 7 days (discharge (adjusted odds ratio 0.28, 95% CI [0.11, 0.71], $P = 0.007$) compared with patients with none or mild oedema. However, there were no significant differences between the two oedema groups in terms of change in glomerular filtration rate at 7 days/discharge (adjusted mean difference 1.944, 95% CI $[-0.862, 4.750]$, $P = 0.175$), in dyspnoea VAS or global well-being VAS. Patients had a similar length of hospital stay (adjusted mean difference 1.11, 95% CI $[-0.37, 2.59]$, $P = 0.143$). The combined endpoint of rehospitalization/death at 60 days in the hospitalized cohort was numerically increased but statistically similar in patients with and without oedema (adjusted hazard ratio 1.44, 95% CI [0.87, 2.39], $P = 0.156$) (Figure 1).

## Discussion

In this study, we compared the clinical characteristics and outcomes between patients with and without oedema in well-characterized ambulatory trial cohorts of patients with HFP EF. In ambulatory patients, the degree of peripheral oedema was associated with a greater body mass and a greater degree of intravascular congestion (as assessed by the JVP). Further, patients with oedema had a worse functional status at baseline with a comparable trajectory at follow-up.

The findings from the stable ambulatory HFP EF cohort extend to the hospitalized population. Higher degree of peripheral oedema was associated with higher intravascular congestion and a greater burden of co-morbid disease, including a higher body mass index. As one would expect, patients with a greater degree of oedema had more fluid removed during the hospital stay, yet the length of stay, dyspnoea, and midterm clinical outcomes did not significantly differ between the two peripheral oedema groups. Notably, the degree of whole-body fluid overload appears to be a poor predictor of symptom burden, functional status, and outcomes. In other words, the absence of oedema does not identify a mild form of HFP EF, as patients have a low functional capacity (median peak VO$_2$ of 14 ml/kg/min) and a high burden of co-morbid disease with a similar burden of HF hospitalizations. Whether peripheral oedema could be
## Table 1 Baseline characteristics by baseline oedema status—ambulatory cohort

| Characteristic | No oedema (N = 165) | Oedema (N = 228) | Unadjusted P-value<sup>a</sup> | Adjusted P-value<sup>b</sup> |
|---------------|----------------------|------------------|-----------------------------|-----------------------------|
| **Demographics** |                      |                  |                             |                             |
| Age, years: median (Q1, Q3) [N] | 67 (59, 75) [165] | 69 (63, 76) [228] | 0.012 | 0.009 |
| Female: n/N (%) | 92/165 (55.8%) | 112/228 (49.1%) | 0.198 | 0.161 |
| Self-reported White race: n/N (%) | 146/165 (89.7%) | 203/228 (89.0%) | 0.777 | 0.451 |
| **Medical history** |                      |                  |                             |                             |
| Atrial fibrillation/flutter<sup>c</sup>: n/N (%) | 69/164 (42.1%) | 111/228 (48.7%) | 0.159 | 0.535 |
| Diabetes mellitus: n/N (%) | 54/165 (32.7%) | 101/228 (44.3%) | 0.028 | 0.015 |
| HF hospitalization in past year: n/N (%) | 48/165 (29.1%) | 64/228 (28.1%) | 0.782 | 0.854 |
| Ischaemic heart disease: n/N (%) | 96/165 (58.2%) | 110/228 (48.2%) | 0.088 | 0.068 |
| **Medications at enrolment** |                      |                  |                             |                             |
| Aldosterone antagonist: n/N (%) | 32/165 (19.4%) | 45/228 (19.7%) | 0.711 | 0.510 |
| ACE inhibitor or angiotensin II receptor blocker: n/N (%) | 107/165 (64.8%) | 145/228 (63.6%) | 0.613 | 0.501 |
| Calcium channel blocker: n/N (%) | 69/165 (42.1%) | 111/228 (48.7%) | 0.044 | 0.111 |
| Loop diuretic: n/N (%) | 4/165 (2.4%) | 8/228 (3.5%) | <0.001 | <0.001 |
| **Laboratory results** |                      |                  |                             |                             |
| Creatinine, mg/dL: median (Q1, Q3) [N] | 1.0 (0.8, 1.3) [163] | 1.2 (0.9, 1.5) [224] | <0.001 | 0.003 |
| NT-proBNP, pg/mL: median (Q1, Q3) [N] | 30.4 (7.7, 734) [164] | 533 (184, 1306) [225] | 0.011 | 0.072 |
| Troponin I, ng/L: median (Q1, Q3) [N] | 0.07 (0.03, 0.22) [163] | 0.12 (0.05, 0.45) [224] | 0.019 | 0.061 |
| **Baseline clinical assessments** |                      |                  |                             |                             |
| Body mass index, kg/m<sup>2</sup> | 23.9 (22.5, 25.3) [165] | 25.4 (23.9, 27.0) [228] | 0.003 | 0.005 |
| Serum albumin, g/L: median (Q1, Q3) [N] | 42.6 (40.0, 45.0) [163] | 42.9 (41.0, 44.5) [224] | 0.827 | 0.805 |
| **Clinical decongestion** |                      |                  |                             |                             |
| Orthopnoea: n/N (%) | 81/160 (50.6%) | 89/217 (41.0%) | 0.107 | 0.084 |
| One pillow (10 cm) | 36/160 (22.5%) | 55/217 (25.3%) | 0.082 | 0.146 |
| Two pillows (20 cm) | 36/160 (22.5%) | 55/217 (25.3%) | 0.082 | 0.146 |
| Three or more pillows | 13/160 (8.1%) | 21/217 (9.7%) | 0.082 | 0.146 |
| **6 min walk distance, m: median (Q1, Q3) [N] | 306 (246, 400) [119] | 304 (214, 375) [182] | 0.082 | 0.146 |
| Peak VO<sub>2</sub>, mL/min: median (Q1, Q3) [N] | 12 (11, 16) [128] | 12 (10, 14) [165] | 0.003 | 0.002 |
| Baseline echocardiography |                      |                  |                             |                             |
| Global longitudinal strain: % | 9.0 (8.3, 9.7) [165] | 9.1 (8.3, 9.7) [228] | 0.726 | 0.762 |
| LV diastolic dimension, cm: median (Q1, Q3) [N] | 4.6 (4.3, 5.1) [102] | 4.7 (4.3, 5.1) [149] | 0.490 | 0.242 |
| LV mass index, g/m<sup>2</sup> | 76.7 (62.7, 89.7) [99] | 76.7 (62.7, 89.7) [146] | 0.543 | 0.440 |
| Relative wall thickness ≥0.42: n/N (%) | 40/99 (40.4%) | 76/146 (52.1%) | 0.072 | 0.125 |
| E/A ratio: median (Q1, Q3) [N] | 1.0 (0.9, 1.7) [85] | 1.1 (0.9, 1.8) [131] | 0.350 | 0.590 |
| LV relaxation septal (medial)—E′: m/s: median (Q1, Q3) [N] | 0.06 (0.05, 0.07) [13] | 0.06 (0.05, 0.08) [169] | 0.281 | 0.146 |
| Filling pressure septal (medial)—E/E′: median (Q1, Q3) [N] | 14.3 (10.4, 20.0) [108] | 15.3 (10.7, 20.0) [164] | 0.553 | 0.896 |
| LA volume index, mL/m<sup>2</sup>: median (Q1, Q3) [N] | 37.8 (30.1, 50.6) [89] | 43.3 (35.2, 57.6) [131] | 0.049 | 0.443 |
| Pulmonary artery systolic pressure: median (Q1, Q3) [N] | 32.4 (29.4, 43.0) [70] | 41.4 (34.2, 49.2) [101] | 0.012 | 0.010 |

ACE, angiotensin-converting enzyme; HF, heart failure; LA, left atrial; LV, left ventricular; MV, mitral valve; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; Q1, first quartile; Q3, third quartile; VO<sub>2</sub>, volume of oxygen consumption.

<sup>a</sup>Adjusted for clinical trial only, using linear, logistic, or cumulative logit regression.

<sup>b</sup>Adjusted for age, gender, race, and clinical trial, using linear, logistic, or cumulative logit regression.

<sup>c</sup>Recorded as atrial fibrillation/flutter in INDIE and as atrial fibrillation/flutter in NEAT and RELAX.

<sup>d</sup>Defined as jugular venous pressure <8 cm H<sub>2</sub>O (not elevated/distended), no orthopnoea, and peripheral oedema < moderate.

<sup>e</sup>Recorded as elevated/distended in INDIE and NEAT and as ≥8 cm H<sub>2</sub>O in RELAX.

<sup>f</sup>Baseline echocardiographic data were only obtained in NEAT and RELAX.
Medical history is closely intertwined with clinical volume overload and the amount of residual congestion in hospitalized patients. It is widely accepted that the extent of extravascular fluid overload is a surrogate of disease severity and right ventricular dysfunction. Approximately 33% of patients in the ASCEND-HF trial either gained weight or did not lose a significant amount of weight (under 1 kg) during hospitalization, despite notable symptom improvement. An increase in central filling pressures occurs in many patients without increased body weight, and volume redistribution may trigger cardiac decompensation in these cases. The disproportionally higher degree of obesity in the fluid overloaded groups emphasizes the contribution of obesity to the congestion phenotypes, where plasma volume expansion is further heightened, promoting increased filtration of fluid out of the vascular space. Our findings are particularly interesting in light of a recently published secondary analysis of the TOPCAT trial. The analysis distinguished three distinct phenotypes based on levels of different biomarkers, which suggested to the authors the presence of distinct phenotypes. Phenotype 2 (older, with stiff arteries, small left ventricle, atrial fibrillation) and Phenotype 3 (obese, diabetic, and with advanced symptoms) were considered to be high-risk HFpEF profiles. Notably, oedema was more common in Phenotype 3. Phenogrouping could be highly relevant in HFpEF given disease heterogeneity and the association of better outcomes seen with the use of mineralocorticoid receptor antagonists in Phenotype 3.

### Table 2 Baseline characteristics by baseline oedema status—hospitalized cohort

| Characteristic                              | ≤Mild oedema (N = 89) | ≥Moderate oedema (N = 249) | Unadjusted P-value | Adjusted P-value |
|---------------------------------------------|-----------------------|-----------------------------|--------------------|------------------|
| Demographics                                |                       |                             |                    |                  |
| Age, years: median (Q1, Q3) [N]             | 73 (61, 81) [89]       | 74 (64, 82) [249]           | 0.621              | 0.993            |
| Female: n/N (%)                             | 40/89 (44.9%)         | 98/249 (39.4%)              | 0.714              | 0.863            |
| Self-reported White race: n/N (%)           | 65/89 (73.0%)         | 202/249 (81.1%)             | 0.214              | 0.217            |
| Medical history                             |                       |                             |                    |                  |
| Atrial fibrillation/flutter<sup>a</sup>: n/N (%) | 54/88 (61.4%)         | 158/249 (63.5%)             | 0.652              | 0.975            |
| Diabetes mellitus: n/N (%)                  | 42/89 (47.2%)         | 135/249 (54.2%)             | 0.561              | 0.523            |
| HF hospitalization in past year: n/N (%)    | 55/88 (62.5%)         | 157/246 (63.8%)             | 0.721              | 0.910            |
| Ischaemic heart disease: n/N (%)            | 47/89 (52.8%)         | 118/249 (47.4%)             | 0.190              | 0.115            |
| Medications at enrolment                    |                       |                             |                    |                  |
| Aldosterone antagonist: n/N (%)             | 12/88 (13.6%)         | 45/249 (18.1%)              | 0.546              | 0.523            |
| ACE inhibitor or angiotensin II receptor blocker: n/N (%) | 45/88 (51.1%)      | 109/249 (43.8%)             | 0.211              | 0.233            |
| Beta-blocker: n/N (%)                       | 66/88 (75.0%)         | 182/249 (73.1%)             | 0.680              | 0.746            |
| Calcium channel blocker: n/N (%)            | 35/88 (39.8%)         | 76/249 (30.5%)              | 0.116              | 0.145            |
| Loop diuretic: n/N (%)                      | 77/88 (87.5%)         | 228/249 (91.6%)             | 0.780              | 0.831            |
| Laboratory results                          |                       |                             |                    |                  |
| Creatinine, mg/dL: median (Q1, Q3) [N]      | 1.4 (1.0, 1.7) [88]   | 1.6 (1.2, 2.0) [242]        | 0.441              | 0.471            |
| NT-proBNP, pg/mL: median (Q1, Q3) [N]       | 2945 (1538, 5906) [88] | 3332 (1757, 6336) [242]    | 0.525              | 0.512            |
| Baseline clinical assessments               |                       |                             |                    |                  |
| Body mass index, kg/m<sup>2</sup>: median (Q1, Q3) [N] | 30.9 (26.8, 36.8) [88] | 34.5 (28.1, 42.2) [243]    | 0.002              | <0.001           |
| Clinical decongestion<sup>b</sup>: n/N (%)  | 4/52 (7.7%)           | 0/198 (0.0%)                | 1.000              | 1.000            |
| Jugular venous pressure: n/N (%)            | <0.001                | <0.001                      |                    |                  |
| <8 cm H<sub>2</sub>O                         | 8/50 (16.0%)          | 4/190 (2.1%)                |                    |                  |
| 8–12 cm H<sub>2</sub>O                      | 18/50 (36.0%)         | 42/190 (22.1%)              |                    |                  |
| 13–16 cm H<sub>2</sub>O                     | 11/50 (22.0%)         | 69/190 (36.3%)              |                    |                  |
| ≥16 cm H<sub>2</sub>O                       | 13/50 (26.0%)         | 75/190 (39.5%)              |                    |                  |
| Left ventricular ejection fraction, %: median (Q1, Q3) [N] | 57 (55, 63) [89]    | 56 (55, 63) [249]           | 0.896              | 0.740            |
| Orthopnoea: n/N (%)                         |                       |                             |                    |                  |
| None                                        | 4/49 (8.2%)           | 19/186 (10.2%)              | 0.919              | 0.841            |
| One pillow (10 cm)                          | 7/49 (14.3%)          | 28/186 (15.1%)              |                    |                  |
| Two pillows (20 cm)                         | 23/49 (46.9%)         | 68/186 (36.6%)              |                    |                  |
| Three or more pillows                       | 15/49 (30.6%)         | 71/186 (38.2%)              |                    |                  |
| Dyspnoea VAS: median (Q1, Q3) [N]           | 55 (40, 75) [87]      | 55 (32, 76) [244]           | 0.514              | 0.595            |
| Global well-being VAS: median (Q1, Q3) [N]  | 43 (25, 62) [51]      | 52 (34, 69) [192]           | 0.026              | 0.033            |

ACE, angiotensin-converting enzyme; HF, heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; Q1, first quartile; Q3, third quartile; VAS, visual analogue scale.

<sup>a</sup>P-values are adjusted for age, gender, race, and clinical trial, using linear, logistic, or cumulative logit regression.

<sup>b</sup>Recorded as atrial fibrillation in ATHENA and as atrial fibrillation/flutter in CARRESS, DOSE, and ROSE.

<sup>c</sup>Defined as JVP < 8 cm H<sub>2</sub>O, no orthopnoea, and peripheral oedema < moderate.
One limitation of our study is the subjective definition of congestion groups based on the lone variable of peripheral oedema. Peripheral oedema served as a surrogate of extravascular but also total body fluid overload and is not necessarily representative of intravascular blood volume. Oedema is present on a continuum, and our approach to dichotomize the population might be insufficient to account for intermediate phenotypes. Additionally, some HF patients accumulate fluid primarily in their abdomen instead of the legs, and our study did not collect data on abdominal distention, thus potentially misclassifying some patients. Symptom burden and functional capacity could be an expression of co-morbidity burden or underlying HF independent of oedema status, and discerning the difference is complicated because of multiple confounders and interrelationship of disease and oedema status. The high prevalence of oedema in the ambulatory cohort is likely reflective of a relatively ‘sensitive’ grading scale for peripheral oedema (trace was counted into the oedema group) and a reflection of rigorous inclusions and exclusion criteria for the ambulatory HFpEF cohorts, which could bias the present population towards a more advanced stage of the disease. Notably, in the hospitalized cohort, there was a gap between time of hospitalization and assessment of baseline characteristics (vast majority of patients were enrolled <24 h of admission), opening a window for intravenous diuretic administration that possibly confounds the assessment of oedema. Differences in body mass may partly be due to congestion rather than excess fat, but this could not explain the differences in the compensated outpatient cohort. Further, the study was limited by a small sample size and potentially insufficient power to detect differences between groups. This particularly may confound interpretation of differences in clinical outcomes. We did not adjust for treatment effect given all trials had a null effect, with different protocols, making the adjustment for treatment arm less relevant.

Peripheral oedema and total body fluid overload are key targets of therapy in HFpEF. We demonstrate that patients with oedema have a greater body mass, a greater co-morbidity burden, and more severe exercise limitations. Patients with oedema have a similar degree of dyspnoea and similar hospital course/outcome despite a greater degree of in-hospital fluid removal. Although our data need to be interpreted in the light of a limited sample size, the significance of volume distribution in acute and chronic HFpEF as well as targeted therapeutic interventions based on HFpEF volume phenotype requires further investigation.

Conflict of interest

M.F. consults for Axon Therapies, Daxor, Edwards Lifesciences, and Galvani. S.J.G. has received a Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis; has received research support from Amgen, AstraZeneca, Bristol Myers Squibb, Merck, and Novartis; serves on advisory boards for Amgen, AstraZeneca, and Galvani; and received a Heart Failure Society of America/Emergency Medicine Foundation Acute Heart Failure Young Investigator Award funded by Novartis.
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**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Hospitalized HfPEF trials key inclusion criteria.

**Table S2.** Ambulatory HfPEF trials key inclusion criteria.

**Table S3.** Hospitalized: *°* ATHENA (documented as): Absent/Trace ... Slight ... Moderate ... Marked.

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