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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Aims Heart failure with preserved ejection fraction (HFpEF) 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 HFpEF 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/m^2 [inter-quartile range, IQR 30.5, 41.6] vs. 31.6 kg/m^2 [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 mL/kg/min, 95% 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 HFpEF 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 HFpEF phenotypes.

Keywords Heart failure; Congestion; Oedema

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Introduction

Vascular and tissue congestion are hallmarks of decompensated 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 (HFpEF) are particularly fluid sensitive and prone to cardiac decompensation.[4] Broadly, two extreme clinical volume phenotypes of HFpEF 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).[5] 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/on–off, we aimed to assess the clinical profile and functional outcomes of these ostensible HFpEF '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 HFpEF.

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),[6] CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure),[7] RELAX (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction),[8] ATHENA (Aldosterone Targeted Neurohormonal Combined With Natriuresis Therapy—HF),[9] ROSE (Renal Optimization Strategies Evaluation),[10] INDIE (Inorganic Nitrite Delivery to Improve Exercise Capacity in Heart Failure With Preserved Ejection Fraction),[11] and NEAT (Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Heart Failure with Preserved Ejection Fraction) trials.[12] Common and rigorous entry criteria were required to verify the diagnosis of HFpEF in the trials, specifically New York Heart Association Class II–IV HF symptoms, left ventricular ejection fraction $\geq$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 VO_2) with cardiopulmonary exercise of $\leq$60% and $\leq$75% predicted, respectively, with peak respiratory exchange ratio $\geq$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 VO_2 (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 HFpEF 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 $\leq$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_2O (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_2O, 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 HFpEF. 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 HFpEF 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 HFpEF, 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[a]	Adjusted *P*-value[b]
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* (%)	148/165 (89.7%)	203/228 (89.0%)	0.777	0.451
Medical history				
Atrial fibrillation/flutter[c]: *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	0.514
ACE inhibitor or angiotensin II receptor	107/165 (64.8%)	145/228 (63.6%)	0.613	0.501
blocker: *n*/*N* (%)				
Beta-blocker: *n*/*N* (%)	108/165 (65.5%)	172/228 (75.4%)	0.044	0.111
Calcium channel blocker: *n*/*N* (%)	40/165 (24.2%)	83/228 (36.4%)	0.012	0.020
Loop diuretic: *n*/*N* (%)	106/165 (64.2%)	181/228 (79.4%)	<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*]	304 (76, 734) [164]	533 (184, 1306) [225]	0.011	0.072
Baseline clinical assessments				
Body mass index, kg/m^2: median (Q1, Q3) [*N*]	31.6 (27.9, 36.3) [165]	35.2 (30.5, 41.6) [228]	<0.001	<0.001
Clinical decongestion[d]: *n*/*N* (%)	62/165 (37.6%)	41/228 (18.0%)	<0.001	<0.001
Jugular venous pressure elevated/distended[e]: *n*/*N* (%)	40/162 (24.7%)	111/222 (50.0%)	<0.001	<0.001
Left ventricular ejection fraction, %:	61 (57, 66) [165]	61 (56, 66) [228]	0.403	0.638
median (Q1, Q3) [*N*]				
Orthopnoea: *n*/*N* (%)			0.107	0.084
None	81/160 (50.6%)	89/217 (41.0%)		
One pillow (10 cm)	36/160 (22.5%)	55/217 (25.3%)		
Two pillows (20 cm)	30/160 (18.8%)	52/217 (24.0%)		
Three or more pillows	13/160 (8.1%)	21/217 (9.7%)		
6 min walk distance, m: median (Q1, Q3) [*N*]	330 (246, 400) [119]	306 (214, 375) [182]	0.082	0.146
Peak VO_2, mL/kg/min: median (Q1, Q3) [*N*]	14 (11, 16) [128]	12 (10, 14) [165]	0.003	0.002
Peak VO_2, mL/min: median (Q1, Q3) [*N*]	1247 (885, 1619) [128]	1158 (977, 1480) [165]	0.691	0.315
Baseline echocardiography[f]				
Global longitudinal strain, %: median (Q1, Q3) [*N*]	−12.5 (−15.6, 13.3) [101]	−11.7 (−16.0, 14.8) [168]	0.726	0.762
Cardiac index, mL/min/m^2: median (Q1, Q3) [*N*]	2397 (2073, 2848) [104]	2384 (2009, 2814) [150]	0.538	0.616
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^2: median (Q1, Q3) [*N*]	76.7 (62.7, 89.7) [99]	78.1 (62.8, 95.4) [146]	0.543	0.440
Relative wall thickness ≥0.42: *n*/*N* (%)	40/99 (40.4%)	76/146 (52.1%)	0.072	0.122
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
MV inflow: decel time at leaf tip, ms: median (Q1, Q3) [*N*]	190 (158, 233) [111]	199 (170, 237) [169]	0.674	0.484
LV relaxation septal (medial)—e′, m/s: median (Q1, Q3) [*N*]	0.06 (0.05, 0.07) [113]	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^2: 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*]	34.2 (29.4, 43.6) [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_2, volume of oxygen consumption.

[a]Adjusted for clinical trial only, using linear, logistic, or cumulative logit regression.

[b]Adjusted for age, gender, race, and clinical trial, using linear, logistic, or cumulative logit regression.

[c]Recorded as atrial fibrillation in INDIE and as atrial fibrillation/flutter in NEAT and RELAX.

[d]Defined as jugular venous pressure <8 cm H_2O (not elevated/distended), no orthopnoea, and peripheral oedema < moderate.

[e]Recorded as elevated/distended in INDIE and NEAT and as ≥8 cm H_2O in RELAX.

[f]Baseline echocardiographic data were only obtained in NEAT and RELAX.

Table 2 Baseline characteristics by baseline oedema status—hospitalized cohort

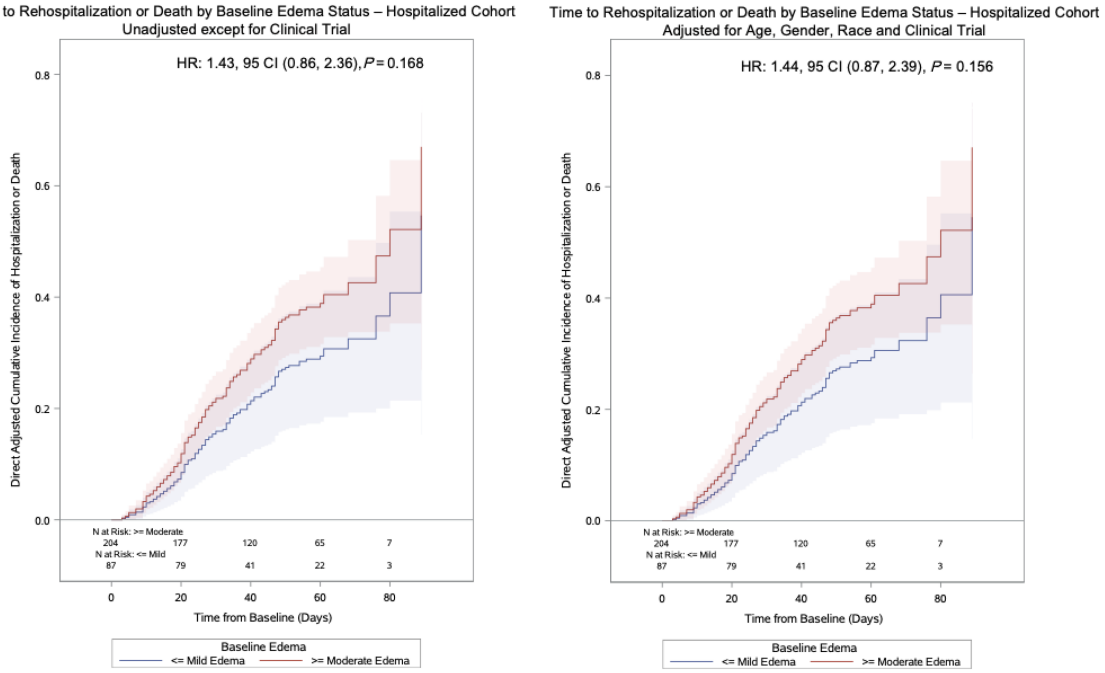
Characteristic	≤Mild oedema (*N* = 89)	≥Moderate oedema (*N* = 249)	Unadjusted *P*-value	Adjusted *P*-value
Demographics				
Age, years: median (Q1, Q3) [*N*]	73 (61, 81) [89]	74 (64, 82) [249]	0.621	0.993
Female: *n*/*N* (%)	40/89 (44.9%)	98/249 (39.4%)	0.714	0.863
Self-reported White race: *n*/*N* (%)	65/89 (73.0%)	202/249 (81.1%)	0.214	0.217
Medical history				
Atrial fibrillation/flutter[a]: *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^2: median (Q1, Q3) [*N*]	30.9 (26.8, 36.8) [88]	34.5 (28.1, 42.2) [243]	0.002	<0.001
Clinical decongestion[b]: *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_2O	8/50 (16.0%)	4/190 (2.1%)		
8–12 cm H_2O	18/50 (36.0%)	42/190 (22.1%)		
13–16 cm H_2O	11/50 (22.0%)	69/190 (36.3%)		
>16 cm H_2O	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* (%)			0.919	0.841
None	4/49 (8.2%)	19/186 (10.2%)		
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.
P-values are adjusted for age, gender, race, and clinical trial, using linear, logistic, or cumulative logit regression.
[a]Recorded as atrial fibrillation in ATHENA and as atrial fibrillation/flutter in CARRESS, DOSE, and ROSE.
[b]Defined as JVP < 8 cm H_2O, no orthopnoea, and peripheral oedema < moderate.

indicative of differing 'volume phenotypes' and not merely a surrogate of disease severity and right ventricular dysfunction in HFpEF needs to be further investigated.

The bedside exam is crucial in the assessment and decision making for hospitalized and ambulatory patients with HF. It is widely accepted that the extent of extravascular volume overload and the amount of residual congestion (in hospitalized patients) is closely intertwined with clinical outcomes.[13] Previous studies have demonstrated that peripheral congestion predicts a worse prognosis.[14,15] However, many patients do not gain a significant amount of weight in the days immediately preceding hospitalization.[2] 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.[16] 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 disproportionately higher degree of obesity in the fluid overloaded groups emphasizes the contribution of obesity to the congestion phenotypes,[17] where plasma volume expansion is further heightened, promoting increased filtration of fluid out of the vascular space.[18] Our findings are particularly interesting in light of a recently published secondary analysis of the TOPCAT trial.[19] 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, and 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.

Figure 1 Clinical outcomes in the hospitalized cohort. CI, confidence interval; HR, hazard ratio.



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

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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.
Defined as for analysis: ≤Mild (Absent/Trace, Slight) vs. ≥Moderate (Moderate, Marked).
° CARRESS (documented as): None … Trace … Moderate … Severe.
Defined as for analysis: ≤Mild (None, Trace) vs. ≥Moderate (Moderate, Severe).
° DOSE (documented as): None … Trace … Moderate … Severe.
Defined as for analysis: ≤Mild (None, Trace) vs. ≥Moderate (Moderate, Severe).
° ROSE (documented as): None … 1+ … 2+ … 3+ … 4+
Defined as for analysis: ≤Mild (None, 1+) vs. ≥Moderate (2+, 3+, 4+)
Ambulatory:
° INDIE (documented as): None … Trace … Mild (1+) … Moderate (2+, 3+) … Severe (4+)
Defined as for analysis: None (None) vs. ≥Trace (Trace, Mild, Moderate, Severe)
° NEAT (documented as): None … Trace … Mild (1+) … Moderate (2+, 3+) … Severe (4+)
Defined as for analysis: None (None) vs. ≥Trace (Trace, Mild, Moderate, Severe).
° RELAX (documented as): None … Trace … Moderate … Severe.
Defined as for analysis: None (None) vs. ≥Trace (Trace, Moderate, Severe).
Table S4. Baseline Peripheral Edema Ambulatory Cohort.
Table S5. Summary of Outcomes by Baseline Edema Status Ambulatory Cohort.

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