European Journal of Internal Medicine 97 (2022) 69–77

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Phenotyping congestion in patients with acutely decompensated heart failure with preserved and reduced ejection fraction: The Decongestion duRing therapY for acute decOmpensated heart failure in HFpEF vs HFrEF-DRY-OFF study

C Cogliati [a], E Ceriani [a,*], G Gambassi [b], G De Matteis [c], S Perlini [d], T Perrone [e], ML Muiesan [f], M Salvetti [f], F Leidi [a], F Ferrara [g], C Sabbà [h], P Suppressa [h], A Fracanzani [i], N Montano [j], E Fiorelli [j], G Tripepi [k], M Gori [l], A Pitino [l], A Pietrangelo [g]

[a] Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli- Sacco, Italy
[b] Department of Medicine and Traslational Surgery, Università Cattolica del Sacro Cuore Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy
[c] Department of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy
[d] Emergency Department, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy
[e] Internal Medicine 1, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy
[f] Department of Clinical and Experimental Sciences, University of Brescia-ASST Spedali Civili Brescia, Brescia, Italy
[g] Department of Internal and Emergency Medicine, University Hospital of Modena, Italy
[h] Division of Internal Medicine and Geriatrics, DIM Department, University of Bari, Italy
[i] Department of Pathophysiology and Transplantation, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy
[j] Department of Clinical Sciences and Health Community, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy
[k] Institute of Clinical Physiology (IFC-CNR), Section of Reggio Calabria, Italy
[l] Institute of Clinical Physiology (IFC-CNR), Section of Rome, Italy

ARTICLE INFO

Keywords:
Acutely decompensated heart failure
Preserved ejection fraction
Reduced ejection fraction
Pulmonary congestion
Intravascular congestion
Lung ultrasound

ABSTRACT

Aims: : To evaluate pulmonary and intravascular congestion at admission and repeatedly during hospitalization for acute decompensated heart failure (ADHF) in HFrEF and HFpEF patients using lung (LUS) and inferior vena cava (IVC) ultrasound.

Methods and results: : Three-hundred-fourteen patients (82±9 years; HFpEF =172; HFrEF=142) admitted to Internal Medicine wards for ADHF were enrolled in a multi-center prospective study. At admission HFrEF presented higher indexes of pulmonary and intravascular congestion (LUS-score: 0.9 ± 0.4 vs 0.7 ± 0.4; $p<0.01$; IVC end-expiratory diameter: 21.6 ± 5.1 mm vs 20±5.5 mm, $p<0.01$; IVC collapsibility index $24.4 \pm 17.4\%$ vs $30.9 \pm 21.1\%$ $p<0.01$) and higher Nt-proBNP values (8010 vs 3900 ng/l; $p<0.001$). At discharge, HFrEF still presented higher B-scores (0.4 ± 4 vs 0.3 ± 0.4; $p = 0.023$), while intravascular congestion improved to a greater extent, thus IVC measurements were similar in the two groups. No differences in diuretic doses, urine output, hemoconcentration, worsening renal function were found. At 90-days follow up HF readmission/death did not differ in HFpEF and HFrEF (28% vs 31%, $p = 0,48$). Residual congestion was associated with HF readmission/death considering the whole population; while intravascular congestion predicted readmission/death in the HFrEF, no association between sonographic indexes and the outcome was found in HFpEF.

Conclusions: : Serial assessment of pulmonary and intravascular congestion revealed a higher burden of fluid overload in HFrEF and, conversely, a greater reduction in intravascular venous congestion with diuretic treatment. Although other factors beyond EF could play a role in congestion/decongestion patterns, our data may be relevant for further phenotyping HF patients, considering the importance of decongestion optimization in the clinical approach.

* Corresponding author at: Department of Biomedical and Clinical Sciences, Ospedale Luigi Sacco, University of Milan, Italy.
E-mail address: elisa.ceriani@asst-fbf-sacco.it (E. Ceriani).

https://doi.org/10.1016/j.ejim.2021.11.010
Received 4 June 2021; Received in revised form 29 October 2021; Accepted 1 November 2021
Available online 26 November 2021

1. Introduction

Acute decompensation of heart failure (ADHF) is the most common reason for hospitalization in patients above the age of 65 years in Western countries [1]. It imposes a significant burden both on patients, due to the high mortality rate, and on health care systems.

Congestion is the cardinal manifestation of ADHF regardless of ejection fraction (EF) [2]. Based on clinical signs, patients with reduced (HFrEF) and preserved (HFpEF) ejection fraction apparently show similar patterns of congestion, despite higher BNP values in HFrEF [3]. However, scanty evidence exists regarding specific markers of intravascular and pulmonary congestion within the two different EF phenotypes.

Echocardiographically derived indexes of intravascular congestion have been found to be not different between HFrEF and HFpEF [3]. In contrast, pilot studies focusing on lung ultrasound reported higher pulmonary congestion in hospitalized HFrEF patients [4, 5]. Moreover, using a quantitative volume analysis based on radiolabeled albumin dilution technique, HFpEF was observed to be characterized by lower intravascular volume expansion at admission, with greater extravascular fluid clearance in response to diuretic therapy[6].

Hence, it remains unclear whether the profiles of congestion differ substantially in HFrEF and HFpEF. Moreover, studies assessing the time course of pulmonary and intravascular congestion indices at regular intervals during hospitalization for ADHF are lacking.

A better understanding of the patterns of congestion might have relevant implications as optimal volume management represents the main clinical challenge in ADHF, where both suboptimal decongestion and excessive volume depletion occurrence might negatively impact prognosis [7, 8, 9].

Thus, in this study we assessed the differential patterns of pulmonary and intravascular congestion and the decongestion kinetics during treatment in a group of ADHF patients with reduced and preserved ejection fraction. For this purpose, we performed serial lung ultrasound (LUS) and inferior vena cava (IVC) assessments for respectively evaluating extravascular lung water and intravascular volume [10]. Moreover, a three months follow-up was obtained for all the patients and the prognostic value of congestion parameters at discharge was evaluated.

2. Methods

2.1. Study design and participating centers

The DRY-OFFstudy (**D**econgestion du**R**ing therap**Y** for acute dec**O**mpensated heart failure in H**F**pEF vs H**F**rEF) is a multi-center prospective study promoted under the auspices of the Italian Society of Internal Medicine (SIMI – Società Italiana di Medicina Interna), to evaluate patients with ADHF admitted to Internal Medicine wards. The participating centers were: Ospedale Luigi Sacco, Milano (coordinating center); IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano; Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; Fondazione I.R.C.C.S. Policlinico San Matteo, Pavia; Ospedale Policlinico Giovanni XXIII, Bari; Ospedale Policlinico di Modena, Modena; Spedali Civili di Brescia, Brescia.

2.2. Patient population

Only patients hospitalized in Internal Medicine wards from the Emergency Department (ED) for ADHF between September 2018 and February 2020, were considered for inclusion in the study. The diagnosis of ADHF was made first by the emergency physician based on HF guidelines [11] and was later confirmed by the attending physician at ward admission, thus enrolling the patients.

Exclusion criteria were: age <18 years; pregnancy; acute coronary syndromes; end-stage renal impairment (clearance <30 mL/min) or dialysis; acute or recent (<3 months) pneumonia; ongoing sepsis; interstitial lung disease; severe pleural effusion (echo-free space ≥4 intercostal spaces at lung ultrasonographic examination); chronic liver disease; bedridden condition; any concomitant cancer. Patients had to be in stable haemodynamic conditions, without needing of inotropic support at the time of ward admission. Finally, no more than 24 h should have elapsed between initial evaluation in the ED and the actual admission to the internal medicine ward.

2.3. Data collection

All patients were admitted to the ward from the Emergency Department. Arterial Blood Gas analysis (ABG), EKG and chest X-ray performed in the ED were collected. At ward admission a complete medical history was collected including possible etiology of heart failure, cardiac and non-cardiac comorbidities. All heart failure-related and other CV medications, presence of intracardiac devices and chronic oxygen treatment were registered. For patients in treatment with diuretics, the average daily dose was registered. Patients were asked about the timing of heart failure diagnosis and about previous HF-related hospitalizations.

At admission in the ward, vital parameters and signs of congestion at physical examination were registered. Moreover, blood was drawn for a complete panel to evaluate total blood counts, glycemia, renal function, electrolytes and liver function tests.

2.4. Echocardiographic examinations

Echocardiographic examinations were performed after patient initial stabilization, by experienced operators of local echocardiography lab.

Measurements of chamber dimensions and cardiac systolic and diastolic function were obtained according to the American Society of Echocardiography guidelines [12, 13]. A conventional cut-off value of 45% was considered to divide patients in two groups: HFrEF patients with EF ≤ 45% and patients with HFpEF those with EF>45%.

Colleagues involved in image acquisition were blinded to NT-proBNP levels, LUS examinations and laboratory values.

2.5. Hospital stay

Every 48 h, the following parameters were registered: vital signs, daily urine output, daily diuretic dosage (either intravenous or oral), a blood tests panel comprehensive of complete blood count, creatinine, urea, electrolytes.

2.6. Clinical, biochemical and ultrasonographic parameters of congestion

CLINICAL - Presence of peripheral edema, pulmonary rales and jugular vein distension were recorded every 48 h in all patients. NYHA class was assessed at discharge.

BIOCHEMICAL - NT-proBNP was measured for the first time at admission and repeated prior to hospital discharge.

Hemoconcentration was considered as marker of decongestion; it was defined as an increase in haematocrit above admission values at any time during the hospitalization, on the basis of blood samples collected every 48 h [14].

ULTRASOUND –LUS and IVC parameters were recorded every 48 h. LUS was performed at bedside with the patient in a semi-supine position, using a convex probe (3.5–5 MHz, lung preset) to quantify pulmonary congestion by detecting B-lines. Ultrasound machines setting were optimized following the subsequent modalities: low mechanical index (0.7 or less); a single focus, positioned on the pleural line; no harmonic modality; no persistence, depth between 10 and 12 cm according to patient constitution.

The chest wall was divided into 11 regions, 5 on the left and 6 on the right, as previously described [15, 16]. Each region was classified according to the presence of B-lines: 'B0' less than 3 B-lines; 'B1' at least 3

B-lines, and 'B2' coalescent B-lines. B-lines estimation was performed using transversal scan and interpreted in a real time manner. The highest score scan in each region was used to assess B-lines burden. A mean B-score was calculated (range 0–2) by dividing the sum of the scores in each area (B0=0, B1=1, B2=2) by the number of regions that could be assessed [17]. Presence of pleural effusion was registered. To obtain a uniform computation of B-scores across different participating centres, a series of training videos produced by the coordinating center was shared in anticipation of the study beginning. Inter-observer variability for B-score evaluation was assessed by an experienced operator of the coordinating center, on loops records of 5% of randomly selected patients. The K value was 0.923.

IVC diameters during expiration (IVC-exp) and inspiration were measured at sub-xyphoid transabdominal long axis 2–3 cm caudal to the right atrial junction with the patient in the supine position. The IVC collapsibility index (IVC-i) was then derived [12].

Investigators performing ultrasound examinations were blind to patients' clinical data and chest X-ray findings. Additionally, physicians in charge of managing the patients had no knowledge of LUS and IVC findings.

2.7. Follow up

Follow-up was performed by contacting patients or their caregivers over the phone 90 days after discharge. All the successive readmissions for AHF or deaths from any cause were considered as "events". Electronic clinical records have been checked to verify the readmission events.

2.8. Outcomes

The study end points were:

- any difference in congestion at admission, discharge and during treatment for acute decompensation in HFpEF vs HFrEF by means of B-score LUS evaluation and IVC measurements.
- any difference in hemoconcentration and worsening renal function (WRF) occurrence in HFpEF vs HFrEF during treatment for acute decompensation. WRF was defined as an increase in serum creatinine of $\geq$ 0.3 mg/dl from baseline at any time point during hospitalization.
- to explore the prognostic role of the following variables in all the patients, in HFpEF and HFrEF subgroup: B score, IVC-exp, IVC-i, NT-proBNP and creatinine value at discharge; hemoconcentration and WRF occurrence; age and gender.

2.9. Ethics approval

Patients were managed by attending physicians according to ADHF guidelines of the European Society of Cardiology, eventually with minimal local adaptation, both in the Emergency Department and in the Internal Medicine wards.

The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of each participating Institution (protocol number of the coordinating center 473/2018).

Written informed consent was obtained for all study participants.

2.10. Statistical analysis

Data were expressed as mean ± standard deviation (normally distributed data), median and inter-quartile range (non-normally distributed data) or as absolute frequency and percentage (binary or ordinal data), as appropriate. Between groups comparisons were performed by independent T-Test (normally distributed data), Mann-Whitney test (non-normally distributed data), or Chi Square Test (binary data). The evolution over time of the ultrasound variables compared between ADHF patients with preserved and reduced EF by Linear mixed models (LMMs) analysis (from time 0 to time 4 onwards). The LMM methodology extends the ordinary least squares linear regression by allowing for random, or cluster-specific effects in the linear predictor. In the LMMs (having the repeated measurements over time of B-score, IVC-exp and IVC-i) we included the preserved and reduced EF, the time, and the Preserved/Reduced EF x time interaction term. If not statistically significant this interaction term, this would imply that the evolutions over time of the 3 sonographic scores (see above) would be not statistically different among them. In LMM, data were expressed as regression coefficients (b), 95% CI of the regression coefficient and P-value.

Univariate and multivariate logistic regression analyses were performed, in all patients and separately in preserved and reduced EF patients, to assess the association between the key risk factors and the combined outcome (mortality or readmission) excluding patients with intra-hospital mortality. Only the variables statistically significant in univariate analysis were entered in multivariate models.

A sensitivity analysis was performed to evaluate results according to the three HF classification, based on EF<40%, ≥40% to ≤50%, >50%. Comparisons among the three independent groups were made by one-way ANOVA and validated through non-parametric methodology on the

Table 1
Study population.

	HFpEF (n 172)	HFrEF (n 142)	P value
Female *n* (%)	112 (65.1)	70 (49.3)	<0.01*
Age *y* (±SD)	82.2 (7.6)	81.3 (9.8)	0.339
BMI *kg/m²* (±SD)	27 (6.39)	26.1 (5.19)	0.009*
HF previous hospitalization *n* (%)	107 (63.7)	99 (73.3)	0.096
HF diagnosis > 18 months *n* (%)	102 (66.2)	95 (77.9)	0.047*
CAD *n* (%)	46 (26.7)	79 (55.6)	<0.001*
Heart valve disease *n* (%)	53 (30.8)	53 (37.3)	0.274
DCM *n* (%)	4 (2.33)	11 (7.7)	0.048*
Other cardiomyopathies# *n* (%)	4 (2.3)	5 (3.5)	0.527
Arterial hypertension *n* (%)	140 (81.4)	99 (69.7)	0.022*
Atrial Fibrillation *n* (%)	95 (55.2)	82 (57.7)	0.739
Diabetes Mellitus *n* (%)	67 (38.9)	54 (38)	0.959
Dyslipidemia *n* (%)	48 (27.9)	48 (33.8)	0.315
Obesity *n* (%)	42 (24.4)	20 (14.08)	0.032*
CKD *n* (%)	60 (34.9)	61 (42)	0.178
COPD *n* (%)	43 (25)	38 (26.8)	0.822
ACE-I / ARB *n* (%)	86 (50)	70 (49.3)	0.991
ARNI *n* (%)	2 (1.2)	6 (4.3)	0.086
Beta-blockers *n* (%)	109 (63.4)	104 (73.2)	0.082
Ivabradin *n* (%)	0 (0)	2 (1.41)	0.118
Digoxin *n* (%)	19 (11.1)	12 (8.4)	0.564
Calcium channel blockers *n* (%)	41 (23.8)	20 (14.1)	0.042*
Nitrate td *n* (%)	33 (19)	23 (16.2)	0.589
Loop diuretics *n* (%)	114 (66.3)	106 (74.6)	0.137
Average dose mg (±SD)	56.7 (56.1)	69.5 (89)	0.211
Thiazide diuretics *n* (%)	11 (6.4)	9 (6.34)	1
Average dose mg (±SD)	17.5 (15.9)	11.11 (7.1)	0.321
Potassium-sparing diuretics *n* (%)	40 (23.3)	30 (21.1)	0.753
Average dose mg (±SD)	45.5 (26.4)	56 (30.2)	0.127
Statin *n* (%)	59 (34.3)	67 (47.2)	0.028*
Anti-platelet agents *n* (%)	45 (26.2)	60 (42.2)	0.004*
Anticoagulants *n* (%)	85 (49.4)	77 (54.2)	0.462
Amiodarone *n* (%)	16 (9.4)	15 (10.6)	0.895
O2 treatment *n* (%)	5 (2.9)	8 (5.6)	0.227
PM *n* (%)	25 (14.5)	26 (18.3)	0.366
ICD *n (%)*	7 (4.1)	24 (16.9)	0.0001*
CRT *n* (%)	3 (1.7)	12 (8.4)	0.005*

BMI: body mass index; HF: heart failure; CAD: coronary artery disease; DCM: dilated cardiomyopathy; CKD: chronic kidney disease (defined as glomerular filtration rate <60 mL/min/1.73 m2 for ≥ 3 months); COPD: chronic obstructive pulmonary disease; ACE-I: angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; PM: pacemaker; ICD: implantable cardioverter defibrillator; CRT-ICD: cardiac resynchronization therapy; obesity was defined as a BMI ≥ 30 kg/m².

hypertrophic or infiltrative of any etiology.

* significant p value.

Table 2
Clinical, biochemical and radiological characteristic of patients at ED and ward admission.

	HFpEF	HFrEF	*P value*
Emergency Department			
ABG			
pH mean (sd)	7.42 ± 0.08	7.42 ± 0.09	0.646
pO2 mean (sd)	72 ± 33	73 ± 26	0.956
pCO2 mmHg mean (sd)	38 ± 9	42 ± 10	0.006*
Lactate mmol/L mean (sd)	3 ± 4	2.2 ± 3	0.081
HCO3- mmol/L mean (sd)	24.7 ± 4.7	26.12 ± 5	0.032*
FiO2% mean (sd)	26.2 ± 15.5	28 ± 16	0.433
EKG			
AF/Flutter n (%)	89 (52.4)	62 (44.6)	0.214
PM activity n (%)	22 (12.9)	29 (20.9)	0.087
Left Bundle Branch Block n (%)	7 (4.1)	17 (12.2)	0.015*
Chest X-ray			
Pleural effusion n (%)	104 (62)	77 (56)	0.280
Interstitial congestion n (%)	90 (54)	86 (62)	0.123
Acute pulmonary edema n (%)	10 (6)	16 (12)	0.078
Ward admission			
Vital parameters and physical examination			
SBP *mmHg* mean (sd)	135 (25)	128 (25)	0.012*
DBP *mmHg* mean (sd)	73 (13)	71 (15)	0.218
HR *bpm* mean (sd)	81 (18)	83 (17)	0.152
Lower limb edema n (%)	116 (67)	97 (69)	0.799
Lung crackles n (%)	135 (78)	118 (84)	0.245
Jugular vein distension n (%)	18 (12)	23 (18)	0.799
Blood count and biochemistry			
Hematocrit% mean (sd)	34.9 (6.3)	35.5 (5.3)	0.222
Hemoglobin *g/dl* mean (sd)	11.3 (2.2)	11.5 (1.8)	0.230
Creatinine *mg/dl* mean (sd)	1.3 (0.7)	1.4 (0.6)	0.706
Urea *mg/dl* mean (sd)	65 (46)	68 (47)	0.379
Bilirubin *mg/dl* mean (sd)	1 (0.5)	1.1 (0.6)	0.364
ALT *U/l* mean (sd)	19 (12)	30 (45)	0.008*
AST *U/l* mean (sd)	23 (9)	32 (43)	0.03*
Na^+ *mmol/l* mean (sd)	140 (3)	141 (4)	0.581
K^+ *mmol/l* mean (sd)	3.9 (0.6)	3.8 (0.5)	0.056
Glycemia mg/dl mean (sd)	106 (45)	120 (54)	0.073
NT-proBNP *ng/l* median (IQR)	3900 (2047–8023)	8010 (3466–17,815)	<0.001*

ABG: arterial blood gas analysis; AF: atrial fibrillation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PM: pacemaker.
* significant p value.

B score, IVC-exp and IVC-i. When significant the overall differences with $p<0.10$, post-hoc tests were performed.

All calculations were made by using standard statistical packages (SPSS for Windows Version 22, Chicago, Illinois - USA; STATA 13 for Windows, College Station, USA, RStudio-1.2.5033.1).

3. Results

Three-hundred-fourteen patients were included in the study; 172 were classified as HFpEF and 142 as HFrEF. Mean age was 82±9 years and there was no significant difference between the two groups (Table 1). Anthropometric and clinical characteristics of the patients are summarized in Table 1.

The average time spent in the ED was similar in the two groups (HFpEF: 14.6 ± 10.1 vs HFrEF: 13.9 ± 10.4 h $p = 0.610$). All patients received iv loop diuretics in the ED and the cumulative dose was lower in HFpEF (52±34 mg vs 72±84 mg; $p = 0.023$). Other therapies administered during ED hospital stay were nitrate (12% of HFpEF and 6% of HFrEF, $p = 0.06$) and non-invasive ventilation support (16% of HFpEF and 11% of HFrEF, $p = 0.25$); one patient in each group needed a short course of amine support. Arterial blood gas test, EKG and chest X-Ray results are shown in Table 2. Mean ED oxygen supplementation (FiO2) was not different in HFpEF compared to HFrEF.

Table 3
Echocardiography results.

	HFpEF	HFrEF	P value
EF biplane% mean (sd)	56.5 (6.6)	34.5 (8)	/
EDV ml/m^2 mean (sd)	69.4 (32.2)	106.3 (55.1)	<0.001*
ESV ml/m^2 mean (sd)	32.6 (16.7)	71.69 (41.1)	<0.001*
IVS thickness *mm* mean (sd)	11.1 (5.8)	10.7 (3.9)	0.627
PW thickness *mm* mean (sd)	9 (3.7)	9.6 (3.4)	0.945
LV diameter *mm* mean (sd)	41.3 (16.2)	49.6 (16.6)	<0.001*
LA Volume Index ml/m^2 mean (sd)	54.18 (25.8)	61.72 (34.7)	0.055
RA Volume Index ml/m^2 mean (sd)	36.15 (21.5)	37.9 (18)	0.569
sPAP *mmHg* mean (sd)	40.4 (14.8)	40.4 (13)	0.984
TAPSE *mm* mean (sd)	17.7 (5.1)	17.1 (11.3)	0.546
RV diameter *mm* mean (sd)	38.1 (8.7)	39.6 (9)	0.235
E/A mean (sd)	1.2 (0.7)	1.4 (1)	0.204
E/E' mean (sd)	13.2 (6)	14.34 (5.3)	0.199
Aortic stenosis at least moderate n (%)	16 (9.3)	18 (12.7)	0.247
Mitral stenosis at least moderate n (%)	5 (2.9)	1 (0.7)	0.352
Aortic regurgitation at least moderate n (%)	18 (10.5)	17 (11)	0.398
Mitral regurgitation at least moderate n (%)	66 (38.4)	59 (41.5)	0.319
Tricuspid regurgitation at least moderate n (%)	61 (35.5)	51 (35.9)	0.767

EF: ejection fraction; EDV: end diastolic volume; ESV: end systolic volume; IVS: interventricular septum; PW: posterior wall; LV: left ventricle; LA: left atrium; RA: right atrium; sPAP: systolic pulmonary artery pressure; TAPSE: tricuspid annular plane systolic excursion; RV: Right Ventricle; E/A: ratio of mitral peak velocity flow in early diastole (E) to peak velocity flow in late diastole (A); E/E': ratio of mitral peak velocity of early diastolic filling (E) to early diastolic mitral annular velocity (E').
* significant p value.

The mean hospital stay was 9.8 ± 5.4 days, with no significant difference between HFpEF and HFrEF patients (10.1 ± 5.5 days and 9.6 ± 5.4 days respectively, $p = 0.488$). The mortality rate during hospitalization was 2% (1.4% for HFpEF vs 2.9% for HFrEF, $p = 0.15$).

3.1. Clinical parameters and laboratory values at admission

As illustrated in Table 2, at admission there were no differences in vital parameters, except for systolic blood pressure values that were significantly higher among patients with HFpEF.

AST and ALT values were higher in HFrEF patients (Table 2).

3.2. Markers of congestion at admission

Upon physical examination, pulmonary rales were present in over 80% and peripheral edema in nearly 70% of patients with no statistical differences between those with HFrEF or HFpEF (Table 3). NT-proBNP values were two-fold higher in HFrEF patients compared to HFpEF (Table 2).

Pulmonary congestion, as quantitated by the mean B score value, was more severe among patients with HFrEF compared to those with HFpEF (0.9 ± 0.4 for HRrEF vs 0.7 ± 0.4 for HFpEF; $p<0.01$, Fig. 1).

A higher IVC-exp and a lower IVC-i characterized HFrEF group, thus indicating a greater intravascular congestion in these patients (21.6 ± 5.1 vs 20±5.5 mm, $p<0.01$; 24.4 ± 17.4% vs 30.9 ± 21.1%, $p<0.01$).

Pleural effusion, as evaluated by LUS, was similarly prevalent in the two groups (57% in HFpEF and 61% in HErEF patients).

3.3. Echocardiography

Echocardiographic examination performed during hospitalization

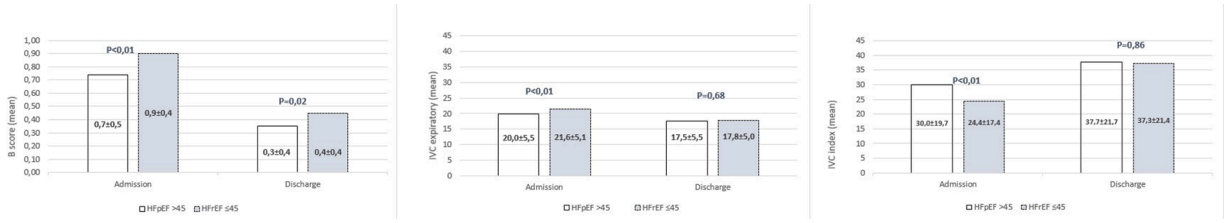

Fig. 1. Left panel: Mean B score value for HFpEF and HFrEF at admission and discharge.
Middle panel: Mean IVC end-expiratory diameter for HFpEF and HFrEF at admission and discharge.
Right panel: Mean IVC collapsibility index value for HFpEF and HFrEF at admission and discharge.

Table 4
Clinical, biochemical and radiological characteristic of patients at discharge.

	HFpEF	HFrEF	*P value*
Physical examination			
SBP *mmHg* mean (sd)	121 (20)	117 (21)	0.078
DBP *mmHg* mean (sd)	67 (12)	67 (12)	0.735
HR *bpm* mean (sd)	73 (16)	75 (14)	0.337
Lower limb edema n (%)	53 (31)	47 (33)	0.659
Lung crackles n (%)	83 (49)	67 (48)	0.818
Jugular vein distension n (%)	9 (5)	7 (5)	0.337
Blood count and biochemistry			
Hematocrit% mean (sd)	36 (6)	37 (5)	0.426
Hemoglobin *g/dl* mean (sd)	12.6 (1.7)	11.8 (1.7)	0.467
Creatinine *mg/dl* mean (sd)	1.38 (0.7)	1.4 (0.6)	0.754
Urea *mg/dl* mean (sd)	70.4 (40.3)	72.3(45)	0.710
Na^+ *mmol/l* mean (sd)	139 (20.5)	139.6 (12.4)	0.749
K^+ *mmol/l* mean (sd)	4 (0.6)	4 (0.7=	0.858
NT-proBNP *ng/l* median (IQR)	2589 (1815–9593)	3884 (1963–10,703)	<0.001*
Hemoconcentration[#]% mean (sd)	3.4 (11.6)	3.9 (11.6)	0.0631
Hemoconcentration occurrence[##] n (%)	122 (70.9)	107 (75.3)	0.380
WRF[§] mg/dl mean (sd)	0.29 (0.4)	0.25 (0.5)	0.384
WRF occurrence [§§] n (%)	38 (22.5)	35 (24.8)	0.629
NYHA class			0.061
I n (%)	25 (16%)	10 (7.5%)	
II n (%)	77 (48%)	61 (46%)	
III n (%)	53 (33%)	51 (39%)	
IV n (%)	5 (3%)	10 (8%)	

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; WRF: worsening renal function.
* significant p value.
# difference between higher hematocrit value during hospitalization and admission hematocrit.
number of patient that developed hemoconcentration, defined as positive delta between higher hematocrit value during hospitalization and admission hematocrit.
§ difference between higher creatine value during hospitalization and admission creatinine.
§§ number of patient that developed WRF, defined as increase in serum creatinine of ≥ 0.3 mg/dl from baseline at any point during hospitalization.

showed significantly lower left ventricle diameters and indexed volumes in HFpEF patients than in HFrEF ones. Other morphological and functional parameters did not show any significant difference in the two HF classes (Table 3).

3.4. Markers of congestion at discharge and their changes during hospital stay

During the hospital stay, patients in both groups received a similar daily dose of loop diuretics (65.2 ± 45.5 mg for HFrEF vs 61.7.±53.2 mg for HFpEF, $p = 0.549$).

Table 4 shows the parameters evaluated at discharge. NYHA class did not differ between HFpEF and HFrEF. Physical signs of pulmonary and peripheral congestion were similar for the two HF subtypes. At discharge, the NT-proBNP values had declined in both groups, remaining higher in HFrEF than in HFpEF patients.

Pulmonary congestion quantified by B-lines was halved in both groups, HFrEF patients still presenting significantly higher B-score values than HFpEF (0.4 ± 4 vs 0.3 ± 0.4; $p = 0.023$) (Fig. 1).

B-score at discharge was significantly related with NYHA class in both groups, with a stronger correlation within the HFrEF group than in the HFpEF one (rho 0.37, $p<0.001$ and rho 0.16, $p = 0.05$ respectively).

Intravascular congestion improved to a greater extent in HFrEF patients (IVC-exp was reduced by 3.7 ± 4.9 mm for HFrEF and by 2.4 ± 5 mm for HFpEF, $p = 0.03$; IVC-i increased from 24.4 ± 17.4 to 37.3 ± 21.5% in HFrEF and from 30±19.8 to 37.7 ± 21.7% in HFpEF patients, p 0.04). As a consequence, at discharge, both the IVC-exp and the IVC-i were similar in the two groups of patients (Fig. 1).

Hemoconcentration occurred in the majority of patients during the hospital stay without any significant difference between the two HF subtypes (71% and 75% for HFpEF and HFrEF, respectively; $p = 0.38$), with a mean increase of 3.4 hematocrit percent points for HFpEF and 3.9 for HFrEF ($p = 0.631$).

WRF occurred in almost one quarter of patients during diuretic treatment, without any difference between those with preserved and reduced ejection fraction (22.5% vs 24.8%; $p = 0.629$). No difference was observed in the cumulative urine output between HFpEF and HFrEF (10.6 ± 7.5 L vs 10.6 ± 6.6 L; $p = 0.992$).

3.5. Patterns and kinetics of decongestion

At each sonographic evaluation performed every 48 h during hospitalization, having an EF > 45% was associated with lower B-score values (Fig. 2). The linear mixed model analysis showed that the evolution over time of both B-score and IVC-exp did not significantly differ ($p = 0.37$ and $p = 0.26$) in patients with and without EF ≤ 45%. Of note, an effect modification by time on the between-groups evolution of IVC-i was found from the second control (T2) onwards (Fig. 2), suggesting a greater relief of intravascular congestion in HFrEF patients, compare to HFpEF, after that point.

3.6. Sensitivity analysis

The sensitivity analysis results are shown in Fig. A.1 and Table A.1 of the Appendix.

Results obtained stratifying population according to three HF categories (EF<40%, EF ranging from 40% to 50%, and EF>50%), displayed an overall significant difference for B-score, IVC-exp and IVC-i at admission ($P<0.01$ for all the variables) (Fig. A.1). Post-hoc tests revealed significant differences only between the extreme groups (EF<40% vs >50%) for the B-score. Similarly, significant differences in IVC-exp and IVC-i mainly emerged between extreme patients' categories. In particular, IVC-exp did not differ between the intermediate class and the lowest one, whereas for the IVC-i did not differ between patients with EF ranging from 40% to 50% and in those with EF>50% (Table A.1). No significant differences were detectable at discharge.

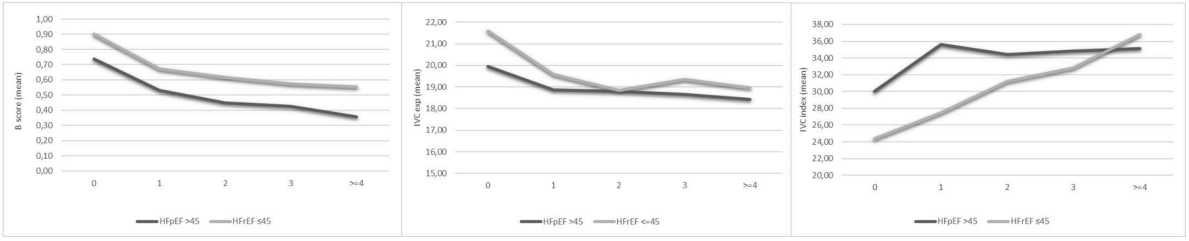

Fig. 2. Mean B score value (left panel), IVC end-expiratory diameter (middle panel) and IVC collapsibility index (right panel) at each ultrasound examination performed during hospitalization. The dark line illustrates the trend in the HFpEF, while the light line shows the trend in the HFpEF. Of notice the first ultrasound was performed within 24 h from admission, while subsequent controls were performed every 48 h. The last point (≥ 4) on the abscissa line identifies the mean value of considered parameters after the fourth ultrasound evaluation, in reason of the small number of patients still hospitalized after this date.
The B score trends show parallel lines for HFpEF and HFrEF, while IVC parameter improved better in HFrEF.

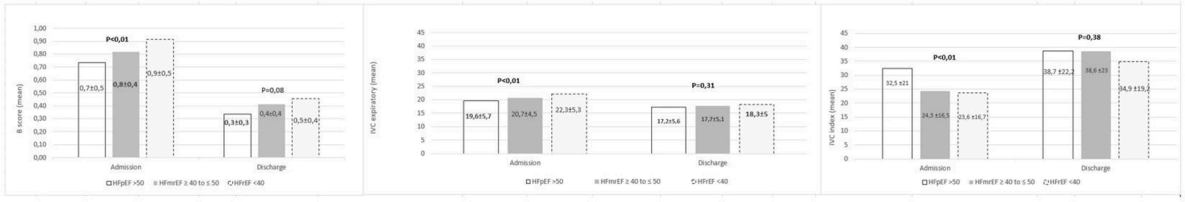

Fig. A.1. Left panel: Mean B score value for HFpEF, HFmrEF and HFrEF at admission and discharge.
Middle panel: Mean IVC end-expiratory diameter for HFpEF, HFmrEF and HFrEF at admission and discharge.
Right panel: Mean IVC collapsibility index value for HFpEF, HFmrEF and HFrEF at admission and discharge.

Finally, the B score at discharge tended to significantly differ ($p = 0.08$) among the three patients' groups and again such a tendence was due to the extreme groups (Table A.1).

3.7. Prognostic factors of the combined outcome (mortality or readmission)

Of the 307 patients discharged alive from hospital, 302 completed the 90 days follow up (167 in the HFpEF and 135 in the HFrEF group). Of them, 56 were hospitalized (32 in the HFpEF group and 24 in the HFrEF) and 33 died (15 in the HFpEF group and 18 in the HFrEF), with no statistical difference of the composite outcome in the two HF subgroup (28% vs 31%; $p = 0.48$).

Univariate and multivariate analyses, in all patients and separately in HFpEF and HFrEF patients, are reported in Table 5.

In the whole cohort of patients, IVC-exp at discharge was independently associated with hospital readmission and death at 90 days, together with discharge creatinine value. The B-score as well as NT-proBNP and WRF occurrence, although significantly associated with the outcome at univariate analysis, were not retained in the multivariate model. These results were partially confirmed for HFrEF patients, where at multivariate analysis IVC-exp and worsening renal function were independently associated with hospitalization/death. Conversely, in HFpEF patients only creatinine at discharge showed a significant and independent association with the combined endpoint.

4. Discussion

The major finding of the DRY-OFF study is not only that patients with HFrEF and HFpEF admitted to Internal Medicine wards for an acute decompensation had different congestion severity, but also that in response to diuretic treatment, the two HF phenotypes showed some differences in the decongestion pattern.

In agreement with the findings by Mayman et al. on HF patients admitted to Internal Medicine units, the mean age of the patients is much higher than those included in clinical trials and even in community-based studies on ADHF [18]. HFpEF patients represent over 50% of the entire cohort, indicating, as previously reported, that the two HF phenotypes are at least equally prevalent among hospitalized patients [19, 20]. The findings of our study show consistent differences in the demographic and clinical characteristics of patients with HFrEF or HFpEF. HFpEF patients were more likely to be female, obese and with a diagnosis of hypertension. Conversely, HFrEF patients were more commonly male, with a diagnosis of coronary artery disease, and presenting with low/normal blood pressure readings [21, 22].

Congestion is a central feature of ADHF and the primary clinical reason for hospitalization, regardless of EF. The current understanding of mechanisms underlying congestion has been mostly based on clinical signs. Moreover, possible differences between HFpEF and HFrEF patients in the patterns at admission and kinetics of decongestion upon diuretic treatment had not been extensively described so far.

LUS is a generally accepted tool to evaluate pulmonary congestion as the B-line burden reflects the degree of extravascular lung water [2, 23]. Ultrasound evaluation of IVC provides information regarding intravascular congestion [24]. Both parameters are more accurate than physical examination, which shows low sensitivity [25]. Moreover, the rapid variation of B-lines and IVC parameters in response to decongestive therapy makes ultrasound a suitable tool for monitoring pulmonary and intravascular congestion [7, 10].

In the DRY-OFF study, at admission, despite comparable clinical and radiological congestion signs, patients with HFrEF appeared to have more severe ultrasonographic signs of intravascular and pulmonary congestion than HFpEF ones. In accordance, the NT-proBNP values were two-fold higher in HFrEF patients. These data, while confirming the low accuracy of clinical as well as chest X-ray signs of congestion, are believed to reflect true pathophysiological differences, as patients in both groups spent an identical time in the ED and, more importantly, the cumulative dosage of loop diuretics in the ED was even higher among HFrEF patients. In fact, even if HFrEF received higher diuretic dosage in the ED, they showed higher values of congestion indexes at ward admission. Our data are in keeping with previous studies on smaller populations reporting greater pulmonary congestion (higher B-line scores) in HFrEF vs HFpEF patients [5,26]. Interestingly, in a recent study, Van Alest et al. failed to demonstrate a difference in some echocardiographic indexes of intravascular congestion between acutely decompensated HFpEF and HFrEF patients, even if BNP values were

Table 5
Prediction of readmission for HF or death from any cause at 90 days: result of univariate and multivariate logistic analyses.

	Univariate		Multivariate	
	All patients			
	OR (95% CI)	P	OR (95% CI)	P
Gender (M vs F)	1.5 (0.91–2.47)	0.11		
Age	1.01 (0.98–1.04)	0.61		
B score at discharge	1.85 (1.00–3.45)	0.05*		
IVC expiratory diameter at discharge	1.07 (1.01–1.12)	0.01*	1.06 (1.01–1.11)	0.03*
IVC index at discharge	0.99 (0.98–1.00)	0.23		
NT-proBNP value at discharge	1.37 (1.05–1.78)	0.02*		
Hemoconcentration occurrence	1.00 (0.98–1.02)	0.93		
Worsening renal function occurrence	2.19 (1.24–3.85)	0.01*		
Creatinine value at discharge	1.76 (1.21–2.55)	<0.001*	1.7 (1.17–2.49)	0.01*
	HFpEF			
	OR (95% CI)	P	OR (95% CI)	P
Gender (M vs F)	1.88 (0.94–3.78)	0.07		
Age	1.00 (0.95–1.04)	0.83		
B score at discharge	2.08 (0.84–5.16)	0.12		
IVC expiratory diameter at discharge	1.03 (0.96–1.09)	0.42		
IVC index at discharge	1.00 (0.99–1.02)	0.84		
NT-proBNP value at discharge	1.21 (0.87–1.69)	0.27		
Hemoconcentration occurrence	1.01 (0.98–1.04)	0.58		
Worsening renal function occurrence	1.94 (0.89–4.25)	0.10		
Creatinine value at discharge	1.78 (1.08–2.93)	0.02*	1.71 (1.04–2.90)	0.04*
	HFrEF			
	OR (95% CI)	P	OR (95% CI)	P
Gender (M vs F)	1.13 (0.55–2.36)	0.74		
Age	1.02 (0.98–1.06)	0.38		
B score at discharge	1.64 (0.69–3.88)	0.26		
IVC expiratory diameter at discharge	1.13 (1.04–1.23)	<0.001*	2.64 (1.12–6.23)	0.03*
IVC index at discharge	0.98 (0.96–1.00)	0.05*		
NT-proBNP value at discharge	1.67 (1.07–2.60)	0.02*		
Hemoconcentration occurrence	0.99 (0.95–1.02)	0.43		
Worsening renal function occurrence	2.48 (1.09–5.65)	0.03*	1.14 (1.04–1.24)	<0.001*
Creatinine value at discharge	1.72 (0.99–3.00)	0.06*		

OR: Odds ratio.
* significant p value.

much higher in HFrEF patients [3]. However, comparisons were made on almost 40 patients for each group, derived from tertiary care facilities, and no information was available about markers of pulmonary congestion.

At discharge, following diuretic treatment, we documented consistent evidence of decongestion both in HFpEF and HFrEF patients. The mean B-score and the mean IVC-exp were reduced and paralleled by a consistent increase in the IVC-i. However, IVC measurements were no longer different between the two groups, because the degree of intravascular decongestion was greater in HFrEF patients. These results didn't substantially change when considering the HF classification in three classes, LVEF<40%, >50% and ≥40% ≤ 50%: differences were mainly driven by the extreme classes with mildly reduced EF patients presenting results in the middle between the two groups.

We can only postulate possible mechanisms contributing to the differences observed in HFpEF vs HFrEF patients. Lower venous compliance and increased arterial resistance have been described in patients with history of hypertension and preserved EF and have been postulated to mainly drive a redistributive mechanism determining pulmonary congestion, often presenting rapidly as "flash" pulmonary edema [27].

However, in our cohort, the intra- and extravascular decongestion in HFpEF patients, obtained without significantly higher WRF occurrence and with a cumulative urinary output similar to HFrEF, allows to hypothesize an effective volume overload and not only a redistributive mechanism of congestion.

On the other hand, the higher residual lung congestion showed by LUS in HFrEF seems to indicate suboptimal decongestion in this group. Potential causes of this residual congestion could be a too early withdrawal of aggressive diuretic therapy, based on an apparently euvolemic condition at physical examination, and/or a potentially smaller 'therapeutic window' in reason of the hypotension occurring in this group.

The different patterns of intravascular decongestion observed in our study seems to be in keeping with previous results. Miller et al. analyzed the variations in volume overload distribution using radiolabeled albumin dilution technique in symptomatic patients with HFrEF or HFpEF [6]. Similar to our findings, patients with HFrEF showed a greater reduction in intravascular volume following diuretic therapy compared to HFpEF patients, whose fluid loss seemed mainly derived from the interstitial lung compartment.

Our results could have several implications for the management of these patients. A better understanding of the entity and distribution of congestion in ADHF with different EF phenotypes could lead to a more 'focused' approach, either in terms of targeting decongestion or in the choice of treatment. Recently, a proposal for a therapeutic approach based on a differential diuretic treatment (natriuretic vs acquaretic) of intravascular and tissue (pulmonary) congestion has been proposed [25]. On the other hand, vasodilators and low diuretic dosage have been shown to be beneficial in some studies. In this regard, better phenotyping HFpEF patients through the finding of a lesser degree of congestion and better differentiation from HFrEF phenotype, might add a further rationale other than symptoms, blood pressure and clinical signs when managing diuretic and/or vasodilator therapy.

Our study brings further support to the notion that US with concomitant quantitation of pulmonary congestion and measurement of

Table A.1
Sensitivity analyses and post-hoc tests.

	B score		IVC-exp	IVC-index
	Admission p value	Discharge p value	Admission p value	Admission p value
Overall	0.01*	0.08#	0.01*	0.01*
HFpEF>50 vs HFrEF<40	0.01*	0.02*	0.00*	0.00*
HFmrEF≥ 40 ≤ 50 vs HFpEF>50	0.16	0.49	0.03*	0.77
HFrEF<40 vs HFmrEF≥ 40 ≤ 50	0.16	0.17	0.14	0.00*

* significant p value.
# in this case post-hoc tests were performed because $p<0.10$.

IVC should be recommended as an informative, quick, easily reproducible and inexpensive tool, not only for the confirmation of the diagnosis, but also for a better quantification of congestion in acutely decompensated HF patients. In this respect, few studies using LUS either alone or in combination with echocardiography to guide therapy in hospitalized HF patients have shown better results in terms of reduction in symptoms of congestion, cardiac filling pressures, blood levels of natriuretic peptides and mean length of hospital stay [26,28]. In the post-hospitalization setting, the use of LUS-guided therapy was associated with a reduced risk of urgent visits for worsening heart failure [29].

Finally, our results confirm HF patients as a high-risk population, considering the 11% mortality and 18% of HF readmission rate at 90 days. As to the prognostic value of the indexes of residual congestion in the whole population, B-lines and IVC-exp were associated with readmission/death, the last one remaining independently predictive for the composite outcome at the multivariate analysis. When considering the two groups, while in HFrEF patients the index of intravascular congestion was confirmed as significantly predictive, no one of the US parameters nor NT-pro-BNP showed a prognostic significance in HFpEF. The results in the whole population analysis are in line with previous studies showing the role of residual congestion in short term prognosis [5, 30]. While HFrEF patients partially resemble these evidences in our population, in HFpEF - at difference with a previous study[7]- residual congestion does not seem to retain a prognostic role. These evidences, although needing a confirmation in larger trials, seem to indicate once again preserved ejection fraction HF as an even more complex condition where comorbidity could act a major role in prognosis [31]. On the other hand, it is possible that extending the follow-up to a longer period could reveal additional information.

Some limitations are worth considering. Age and comorbidity could to some extent introduce undetermined pathophysiological variables possibly even playing a role in congestion/decongestion mechanisms. Nevertheless, our population reflects the progressively increasing mean age of heart failure patients, in particular in Internal Medicine wards. Noticeably, in Italy, Internal Medicine wards admit the great majority of acutely decompensated heart failure patients [32].

The quantitation of B-lines by different investigators in participating centers might have produced somewhat heterogeneous estimates. Recent studies on B-lines image acquisition reported that reproducibility between raters and transducers are scares, being strongly dependent on technical factors, as well on operator interpretation [33, 34]. However, investigators received a common training on the US protocol and device settings, and inter-observer reproducibility has shown excellent reliability. Also, B-lines are a very sensitive but rather non-specific signs of interstitial lung disease, but their repeated evaluation, using the same ultrasound and technical protocol, allows to obtain reliable information regarding modifications in the single patient. Moreover, we have been very careful in excluding patients with lung diseases or other conditions hampering the quantitation of B-lines and, anyway, this issue is less relevant in patients with an already established diagnosis of ADHF.

5. Conclusions

In patients hospitalized with ADHF, the concomitant and serial assessment of pulmonary and intravascular congestion has revealed a different burden of fluid overload between HFpEF and HFrEF phenotypes. Moreover, in response to diuretic treatment, despite superimposable clearance of lung congestion, patients with HFrEF underwent a greater reduction in intravascular venous congestion than HFpEF patients.

Overall, these findings enhance the knowledge about congestion in ADHF patients with different EF phenotypes, previously based on clinical and radiological signs of congestion. Although other factors beyond EF could play a role in congestion/decongestion patterns, we think our data may be of clinical importance for the optimization of decongestion with diuretic treatment. Further studies will have to investigate the time course of the different pathophysiological alterations leading to congestion and the distinct pathogenetic mechanisms involved in acute HF. Finally, novel treatment strategies for relieving pulmonary congestion are currently being investigated and they might lead to a more personalized approach to the treatment of congestion in acute heart failure.

6. Funding

None.

Conflict of interest

None.

Acknowledgements

Members of the SIMI-DRYOFF collaborators:

Popescu Janu V, Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli- Sacco, Italy;

Bartoli A, Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli- Sacco, Italy;

Altieri A, Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli- Sacco, Italy;

Monticelli P, Department of Biomedical and Clinical Sciences, University of Milan, ASST Fatebenefratelli- Sacco, Italy;

Burzo ML, Department of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy;

Della Polla DA, Department of Internal Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy;

Secco G, Emergency Department, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Bracchi F, Emergency Department, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Roberta Mussinelli, Amyloidosis Research and Treatment Center, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Pistoia M, Internal Medicine 1, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Fiengo A, Internal Medicine 1, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Sabatini U, Internal Medicine 1, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Padovini L, Internal Medicine 1, Fondazione IRCCS, Policlinico San Matteo, Pavia, Italy;

Laura Verzeri, Department of Clinical and Experimental Sciences, University of Brescia-ASST Spedali Civili Brescia, Brescia, Italy;

Claudio Mutti, Department of Clinical and Experimental Sciences, University of Brescia-ASST Spedali Civili Brescia, Brescia, Italy;

Giovanni Sacca, Department of Clinical and Experimental Sciences, University of Brescia-ASST Spedali Civili Brescia, Brescia, Italy;

Tomassoli G, Department of Internal and Emergency Medicine, University Hospital of Modena, Italy;

Baldini M, Department of Internal and Emergency Medicine, University Hospital of Modena, Italy;

Lenato GM, Division of Internal Medicine and Geriatrics, DIM Department, University of Bari, Italy;

Peta J, Department of Clinical Sciences and Health Community, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy;

Tiraboschi S, Department of Pathophysiology and Transplantation, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Italy;

Pisano G, Department of Pathophysiology and Transplantation, University of Milan, Fondazione IRCCS Ca' Granda, Ospedale Maggiore

Policlinico, Italy.

References

[1] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, De Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jiménez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, MacKey RH, Magid DJ, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, et al. Heart disease and stroke statistics-2016 update a report from the American Heart Association. *Circulation* 2016;133. e38–e48.

[2] Picano E, Gargani L, Gheorghiade M. Why, when, and how to assess pulmonary congestion in heart failure: pathophysiological, clinical, and methodological implications. Heart Fail Rev 2010;15:63–72.

[3] Van Aelst LNL, M Arrigo, Placido R, Akiyama E, Girerd N, Zannad F, Manivet P, Rossignol P, Badoz M, Sadoune M, Launay JM, Gayat E, Lam CSP, Cohen-Solal A, Mebazaa A, Seronde MF. Acutely decompensated heart failure with preserved and reduced ejection fraction present with comparable haemodynamic congestion. Eur J Heart Fail 2018;20:738–47.

[4] Coiro S, Porot G, Rossignol P, Ambrosio G, Carluccio E, Tritto I, Huttin O, Lemoine S, Sadoul N, Donal E, Zannad F, Girerd N. Prognostic value of pulmonary congestion assessed by lung ultrasound imaging during heart failure hospitalisation : a two- centre cohort study. Nat Publ Gr 2016:1–8.

[5] Palazzuoli A, Ruocco G, Beltrami M, Nuti R, Cleland JG. Combined use of lung ultrasound, B-type natriuretic peptide, and echocardiography for outcome prediction in patients with acute HFrEF and HFpEF. Clin Res Cardiol 2018.

[6] Miller WL, Mullan BP. Volume Overload Profiles in Patients With Preserved and Reduced Ejection Fraction Chronic Heart Failure: are There Differences? A Pilot Study. JACC Hear Fail 2016;4:453–9.

[7] Platz E, Merz AA, Jhund PS, Vazir A, Campbell R, McMurray JJ. Dynamic changes and prognostic value of pulmonary congestion by lung ultrasound in acute and chronic heart failure: a systematic review. Eur J Heart Fail 2017;19:1154–63.

[8] Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010;122:265–72.

[9] Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, Piovanelli B, Carubelli V, Bugatti S, Lombardi C, Cotter G. Dei Cas L. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Hear Fail 2012;5:54–62.

[10] Price S, Platz E, Cullen L, Tavazzi G, Christ M, Cowie MR, Maisel AS, Masip J, Miro O, McMurray JJ, Peacock WF, Martin-Sanchez FJ, Di Somma S, Bueno H, Zeymer U, Mueller C. Expert consensus document: echocardiography and lung ultrasonography for the assessment and management of acute heart failure. Nat Rev Cardiol 2017;14:427–40. Nature Publishing Group.

[11] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Der Meer P Van, Sisakian HS, Isayev E, Kurlianskaya A, Mullens W, Tokmakova M, Agathangelou P, Melenovsky V, Wiggers H, Hassanein M, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016 2016;37:2129–2200m.

[12] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.

[13] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Popescu BA, Waggoner AD. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: an Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277–314.

[14] Boyle A, Sobotka PA. Redefining the Therapeutic Objective in Decompensated Heart Failure: hemoconcentration as a Surrogate for Plasma Refill Rate. J Card Fail 2006;12:247–9.

[15] Volpicelli G, Caramello V, Cardinale L, Mussa A, Bar F, Frascisco MF. Bedside ultrasound of the lung for the monitoring of acute decompensated heart failure. Am J Emerg Med 2008;26:585–91.

[16] Platz E, Jhund PS, Girerd N, Pivetta E, McMurray JJV, Peacock WF, Masip J, Martin-Sanchez FJ, Miró Ò, Price S, Cullen L, Maisel AS, Vrints C, Cowie MR, DiSomma S, Bueno H, Mebazaa A, Gualandro DM, Tavares M, Metra M, Coats AJS, Ruschitzka F, Seferovic PM, Mueller C. Expert consensus document: reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. Eur J Heart Fail 2019;21:844–51.

[17] Cortellaro F, Ceriani E, Spinelli M, Campanella C, Bossi I, Coen D, Casazza G, Cogliati C. Lung ultrasound for monitoring cardiogenic pulmonary edema. *Intern Emerg Med* Springer Milan 2017;12:1011–7.

[18] Maymon SL, Moravsky G, Marcus G, Shuvy M, Pereg D, Epstein D, Litovchik I, Fuchs S, Minha S. Disparities in the characteristics and outcomes of patients hospitalized with acute decompensated heart failure admitted to internal medicine and cardiology departments: a single-centre, retrospective cohort study. ESC Hear Fail 2020;8:390–8.

[19] Goyal P, Almarzooq ZI, Horn EM, Karas MG, Sobol I, Swaminathan RV, Feldman DN, Minutello RM, Singh HS, Bergman GW, Wong SC, Kim LK. Characteristics of Hospitalizations for Heart Failure with Preserved Ejection Fraction. Am J Med 2016;129. 635.e15-26.

[20] Quiroz R, Doros G, Shaw P, Liang CS, Gauthier DF, Sam F. Comparison of characteristics and outcomes of patients with heart failure preserved ejection fraction versus reduced left ventricular ejection fraction in an urban cohort. Am J Cardiol 2014;113:691–6.

[21] Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:1242–54.

[22] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, Treatments, and Outcomes of Patients With Preserved Systolic Function Hospitalized for Heart Failure. A Report From the OPTIMIZE-HF Registry. J Am Coll Cardiol 2007;50:768–77.

[23] Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein DA, Mathis G, Kirkpatrick AW, Melniker L, Gargani L, Noble VE, Via G, Dean A, Tsung JW, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby JJ, Arbelot C, Liteplo A. Sargsya TILC on LU (ILC-L for ICC on LU (ICC-L, Volpicelli G, Elbarbary M, Blaivas M, Lichtenstein D, Mathis G, Kirkpatrick A, Melniker L, Gargani L, Noble V, Via G, Dean A, Tsung J, Soldati G, Copetti R, Bouhemad B, Reissig A, Agricola E, Rouby J, Arbelot C, Liteplo A, Sargsyan A, Silva F, Hoppmann R, Breitkreutz R, Seibel A, Neri L, Storti E, Petrovic T, International Liaison Committee on Lung Ultrasound (ILC-LUS) for International Consensus Conference on Lung Ultrasound (ICC-LUS). International evidence-based recommendations for point-of-care lung ultrasound. Intensive Care Med 2012;38:577–91.

[24] Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, Dickstein K, Drazner MH, Fonarow GC, Jaarsma T, Jondeau G, Sendon JL, Mebazaa A, Metra M, Nieminen M, Pang PS, Seferovic P, Stevenson LW, Van Veldhuisen DJ, Zannad F, Anker SD, Rhodes A, McMurray JJV, Filippatos G. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European society of cardiology and endorsed by the European society of intensive care medicine. Eur J Heart Fail 2010;12:423–33.

[25] Boorsma EM, Maaten JM ter, Damman K, Dinh W, Gustafsson F, Goldsmith S, Burkhoff D, Zannad F, Udelson JE, Voors AA. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. Nat Rev Cardiol 2020; 17:641–55.

[26] Mozzini C, Di Dio Perna M, Pesce G, Garbin U, Fratta Pasini AM, Ticinesi A, Nouvenne A, Meschi T, Casadei A, Soresi M, Cominacini L. Lung ultrasound in internal medicine efficiently drives the management of patients with heart failure and speeds up the discharge time. Intern Emerg Med 2018;13:27–33.

[27] Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure - *Re*-distribution and other mechanisms beyond fluid accumulation. Eur J Heart Fail 2008;10:165–9.

[28] Öhman J, Harjola VP, Karjalainen P, Lassus J. Focused echocardiography and lung ultrasound protocol for guiding treatment in acute heart failure. ESC Hear Fail 2018;5:120–8.

[29] Araiza-Garaygordobil D, Gopar-Nieto R, Martinez-Amezcua P, Cabello-López A, Alanis-Estrada G, Luna-Herbert A, González-Pacheco H, Paredes-Paucar CP, Sierra-Lara MD, Briseño-De la Cruz JL, Rodriguez-Zanella H, Martinez-Rios MA A-MA. A randomized controlled trial of lung ultrasound-guided therapy in heart failure (CLUSTER-HF study). Am Hear J 2020;227:31–9.

[30] Akhabue E, Pierce JB, Davidson LJ, Prenner SB, Mutharasan RK, Puthumana JJ, Shah SJ, Anderson AS, Thomas JD. A Prospective Pilot Study of Pocket-Carried Ultrasound Pre- and Postdischarge Inferior Vena Cava Assessment for Prediction of Heart Failure Rehospitalization. J Card Fail 2018:24.

[31] Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med 2015;175.

[32] Maggioni AP, Orso F, Calabria S, Rossi E, Cinconze E, Baldasseroni S, Martini N. The real-world evidence of heart failure: findings from 41 413 patients of the ARNO database. Eur J Heart Fail 2016;18:402–10.

[33] Gullett J, Donnelly JP, Sinert R, Hosek B, Fuller D, Hill H, Feldman I, Galetto G, Auster M, Hoffmann B. Interobserver agreement in the evaluation of B-lines using bedside ultrasound. *J Crit Care* W.B. Saunders 2015;30:1395–9.

[34] Mento F, Demi L. On the influence of imaging parameters on lung ultrasound B-line artifacts. in vitro study . *J Acoust Soc Am* Acoustical Society of America (ASA) 2020; 148:975–83.