








Distinct clinical phenotypes of congestion in acute heart failure: characteristics, treatment response, and outcomes

Justyna Maria Sokolska^{1,2*} , Mateusz Sokolski^{1,3} , Robert Zymliński^{1,3} , Jan Biegus^{1,3} , Paweł Siwołowski^{1,4} , Sylwia Nawrocka-Millward³, Katarzyna Swoboda⁴, Piotr Gajewski^{1,3}, Ewa Anita Jankowska^{1,3} , Waldemar Banasiak⁴ and Piotr Ponikowski^{1,3} 

¹Department of Heart Diseases, Wrocław Medical University, ul. Borowska 213, Wrocław, 50-556, Poland; ²Department of Cardiology, University Heart Center, University Hospital Zurich, Zürich, Switzerland; ³Centre for Heart Diseases, University Hospital, Wrocław, Poland; ⁴Centre for Heart Diseases, Clinical Military Hospital, Wrocław, Poland

Abstract

Aims Patients with acute heart failure (AHF) are included into clinical trials regardless of differences in baseline clinical characteristics. The aim of this study was to assess patients with AHF according to the presence of central and/or peripheral congestion at hospital admission and evaluate treatment response and outcomes in studied phenotypes.

Methods and results We investigated retrospectively 352 patients (mean age: 68 ± 13 years, 77% men) hospitalized due to AHF with the signs of congestion on admission. Patients were divided according to the type of signs of congestion into three groups: A, isolated pulmonary congestion (*n* = 52, 15%); B, isolated peripheral congestion (*n* = 31, 9%); and C, signs of mixed (peripheral and central) congestion (*n* = 269, 76%). Patients from Group A had lower concentration of urea, bilirubin, and gamma-glutamyl transferase whereas higher level of haematocrit, albumin, and leukocytes on admission. The highest baseline N-terminal pro-B-type natriuretic peptide level (median: 4113 vs. 3634 vs. 6093 pg/mL) and percentage of patients with chronic heart failure (56 vs. 58 vs. 74%; A vs. B vs. C, respectively, all *P* < 0.01) were observed in Group C. There were no differences in terms of demographics, co-morbidities, left ventricular ejection fraction, and applied treatment between studied groups. Patients from Group A had the highest systolic blood pressure on admission (145 ± 37 vs. 122 ± 20 vs. 130 ± 29 mmHg) and the biggest decrease in systolic blood pressure [−22 (−45 to −4) vs. −2 (−13 to 2) vs. −10 (−25 to 0) mmHg] and heart rate [−16 (−35 to −1.5) vs. −1 (−10 to 5) vs. −7 (−20 to 0) b.p.m.] with the lowest weight change [−1.0 (−1.0 to 0) vs. −2.9 (−3.8 to −0.9) vs. −2.0 (−3.0 to −1.0) kg; all *P* < 0.01] after 48 h of hospitalization. There were differences in short-term and long-term outcomes with favourable results in Group A. Group A experienced less frequent in-hospital heart failure worsening during the first 48 h (4 vs. 23 vs. 7%), had shorter length of hospital stay [6 (5–8) vs. 7 (5–11) vs. 7 (6–11) days], and had lower 1 year all-cause mortality (12 vs. 28 vs. 29%; all *P* < 0.05). Presence of peripheral congestion on admission was independent predictor for all-cause mortality within 1 year [hazard ratio (95% confidence interval): 2.68 (1.06–6.79); *P* = 0.04].

Conclusions Patterns of congestion in AHF are associated with differences in clinical characteristics, treatment response, and outcomes. It needs to be considered once planning clinical trials in AHF.

Keywords Heart failure; Cardiac failure; Congestive heart failure; Clinical trials; Signs and symptoms

Received: 9 January 2020; Revised: 10 August 2020; Accepted: 11 August 2020

*Correspondence to: Justyna Sokolska, Department of Heart Diseases, Wrocław Medical University, ul. Borowska 213, 50-556 Wrocław, Poland. Tel: +48 71 733 11 12. Email: justyna.sokolska@umed.wroc.pl

Introduction

The last decades have witnessed recurrent disappointments of clinical trials in introducing novel treatment strategies, all

of which have not improved the outcomes of patients with acute heart failure (AHF).^{1,2} A heterogeneity of population is widely considered to be the most important reason for neutral findings of these trials.^{3–5} Therefore, accurate

profiling of patients admitted with AHF generates considerable interest in terms of designing clinical trials in the clinical settings of AHF.^{6–10}

Current European Society of Cardiology (ESC) Guidelines for diagnosis and treatment of acute and chronic heart failure (HF) recommend to classify patients with AHF according to clinical profiles, based on the presence or absence of congestion ('wet' vs. 'dry') and peripheral hypoperfusion ('cold' vs. 'warm') during bedside physical examination.^{1,11,12} Prognostic value of the aforementioned clinical profiling has been recently confirmed.^{6–8}

Fluid overload leading to congestion is the most common underlying cause of clinical deterioration in patients with HF, with frequent subsequent need for hospital admission. Patterns of fluid overload development (i.e. gradual vs. rapid), localization and magnitude of congestion, and its response to the therapy all are important elements for clinical evaluation of patients admitted with AHF. Despite growing interest in clinical classification of AHF, characteristics of different profiles of congestion and their associations with presence, severity, and duration of HF signs and symptoms, as well as therapeutic and prognostic impact, have not been established. Therefore, the aim of this study was to link the presence of different types of congestion at hospital admission with clinical characteristics, treatment response, and outcomes.

Methods

Study population

The studied population consisted of patients recruited for two AHF registries that run at our institution between 2010–2012 and 2016–2017. In this study, we evaluated patients with signs of congestion at hospital admission.

Patients were treated in accordance with the recommendations of the ESC Guidelines.^{1,13,14} Other inclusion and exclusion criteria are listed in our previous references.^{15, 16} In particular, for this analysis, to minimize the chance of imprecise interpretation of physical examination (see succeeding text) due to other differential diagnoses, patients with a history of severe pulmonary disease and advanced liver and renal disease were excluded.

The study protocol was approved by the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Study design

After inclusion into the study, information on demographics, co-morbidities, and clinical history was collected together

with careful physical examination (for details, see succeeding text).

On admission at the emergency department (as a part of a standard AHF care), venous blood samples were obtained from all studied patients and subsequently after 24 and 48 h. The following laboratory measurements were assessed using standard methods in our laboratory: (i) haematology: haemoglobin (g/dL), haematocrit (%), and leukocytes (white blood cell, g/dL); (ii) electrolytes: sodium (mEq/L) and potassium (mEq/L); (iii) renal and liver function tests: serum creatinine (mg/dL), urea (mg/dL), estimated glomerular filtration rate (mL/min/1.73 m²), bilirubin (mg/dL), aspartate transaminase (IU/L), alanine transaminase (IU/L), gamma-glutamyl transferase (IU/L), and albumin (mg/dL); (iv) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP, pg/mL) using an immunoenzymatic method (Siemens, Germany); (v) high-sensitivity cardiac troponin I (ng/mL) using chemiluminescence (technology LOCI) on Dimension EXL System (Siemens Healthcare Diagnostics, Erlangen, Germany); (vi) C-reactive protein (CRP, mg/L) using an immunoturbidimetric method (KoneLab 30, Finland); and (vii) acid–base balance in the capillary blood sample.

Echocardiography was performed at the discretion of treating physician.

Definitions

Patients were divided according to the type of signs of congestion on admission to hospital into three groups:

- A patients with isolated signs of pulmonary congestion;
- B patients with isolated signs of peripheral congestion; and
- C patients with signs of mixed congestion (central and peripheral congestion).

Accurate physical examination of patients with AHF on admission to hospital was essential for their proper classification into the studied phenotypic groups (Groups A–C). Therefore, to ensure high standard quality of physical examination in our study, we undertook the following measures:

- a clinical examination was always performed in a standardized manner with precisely described definitions of physical findings, which were applied by a physician to classify correct signs of AHF in studied population; and
- b in all cases, clinical assessment was either performed or supervised by a cardiologist experienced in HF management.

Pulmonary congestion was defined as any rales heard over the lung fields that persisted after a cough in attempt to clear. It was classified as *mild* (heard in the lower 1/3 of either or both lung fields), *moderate* (rales heard throughout the

lower half to 2/3 of either or both lung fields) or *severe* pulmonary congestion (rales heard throughout more than 2/3 of either or both lung fields). Lack of pulmonary congestion was defined as no rales heard anywhere in the lung fields, including patients with transient rales that needed an initial clearing with cough.

Testing for pleural effusion was not included in the definition of pulmonary congestion.

Peripheral congestion was defined as a detection of limited areas where mild digital pressure elicits an indentation of skin and subcutaneous tissues on lower extremities or sacrum, if subject has been recumbent, presence of jugular vein distention, hepatic enlargement, or ascites. It was classified as *mild* oedema (limited to feet and ankles, which resolves over approximately 10–15 s), *moderate* peripheral oedema (that disappears slowly after 15–30 s or more), and *severe* peripheral oedema (oedema extended to lower legs or thighs, being easily produced and slowly resolving in more than 30 s) with/without jugular vein distention and/or hepatomegaly and/or ascites.

In order to minimize the chance of the other differential diagnoses to affect the interpretation of the findings of congestion, in all uncertain cases, they were confronted with patients' history, laboratory findings, or chest X-ray results.

On admission, after 24 and 48 h of hospitalization, patients were asked to assess severity of dyspnoea at rest by using a self-reported *10-point Likert scale*, where 0 means 'lack of dyspnoea' and 10 points means 'dyspnoea of the worst severity/maximal dyspnoea'. Ten-point Likert scale was chosen as well-validated practical tool widely applied in the clinical settings of AHF.

In order to identify a biochemical evidence of myocardial damage and alterations in congestion status, we analysed changes in cardiac biomarkers (troponin I and NT-proBNP) during the first 48 h of hospitalization in studied groups using an approach described in our previous publication.¹⁷

The following endpoints were assessed in the study:

- in-hospital HF worsening, defined as a presence of deterioration or lack of relevant improvement in clinical status despite optimized therapy during the first 48 h of hospitalization, assessed by a treating physician (after exclusion of one patient, who died during the first 48 h of hospitalization);
- duration of index hospitalization (after exclusion of 12 patients, who died in hospital); and
- all-cause mortality during the 365 days of follow-up (including in-hospital mortality).

Information regarding survival was obtained directly from the patients or their families during phone calls, HF clinic database, or from the hospital system, after 1 year from the admission.

The length of follow-up of the patients in whom an event occurred after 1 year, and in all survivors, was censored at 365 days. Four patients (1%) were lost to follow-up.

Statistical analysis

The assumption of normality was assessed for all studied parameters using the Kolmogorov–Smirnov test. Normally distributed continuous variables were expressed as means \pm standard deviations. Variables with a skewed distribution were expressed as medians with lower and upper quartiles and were log transformed in order to normalize their distributions. The categorical variables were presented as numbers and percentages. The statistical significance of differences between the groups was tested using analysis of variance (the Kruskal–Wallis test with adequate post-tests) or the χ^2 test, where appropriate.

To establish the effect of peripheral congestion on survival (i.e. considering patients who belong to Groups B or C together as having this risk factor), we performed Cox proportional hazard regression models. Presence of peripheral congestion and other clinical variables were determining variables (predictors), while the endpoint was clinical status at the end of follow-up (dead/alive). The follow-up of patients who survived over 1 year was censored at 365 days. The associations between signs of peripheral congestion and survival were adjusted in multivariable models for subsequent variables that were statistically significant predictors in univariable models. The interaction tests between prognostic indicators were performed, and variables that demonstrated significant interrelation were excluded from the model.

The Kaplan–Meier curves for cumulative survival were constructed to estimate the effect of the physical signs of AHF on 12 months all-cause mortality.

Because of the fact that our study was a secondary analysis of a pre-set database, it was not possible to execute a sample size calculation a priori.

A value of $P < 0.05$ was considered as statistically significant. Alpha was not corrected for multiple comparisons. Statistical analyses were performed using the STATISTICA 13.3 data analysis software system (StatSoft, Inc.).

Results

We investigated 352 patients hospitalized due to AHF with signs of congestion. Patients with AHF were mainly men ($n = 271$; 77%), with mean age of 68 ± 13 years, history of chronic HF ($n = 240$; 69%), and mainly ischaemic aetiology of HF ($n = 182$; 54%). After admission, 104 (30%) patients were treated at the cardiac intensive care unit and subsequently transferred after clinical stabilization to the

Table 1 Baseline characteristics of patients with acute heart failure according to signs of congestion on admission

	A Isolated signs of lung congestion (n = 52)	B Isolated signs of peripheral congestion (n = 31)	C Signs of lung and peripheral congestion (n = 269)	P
Demographics and clinical variables				
Age (years)	65 ± 13	67 ± 12	67 ± 13	0.51
Male, n (%)	34 (65)	24 (77)	215 (79)	0.10
LVEF (%)	30 (25–40)	35 (28–55)	30 (23–45)	0.21
HFpEF/HFmrEF/ HFrEF (%)	15/18/67	31/15/54	20/12/68	0.47
Medical history				
HF de novo, n (%)	23 (44)	13 (42)	70 (26)	0.006 (b, c)
Ischaemic HF aetiology, n (%)	28 (56)	15 (50)	140 (54)	0.87
Hypertension, n (%)	42 (81)	22 (73)	191 (72)	0.42
Atrial fibrillation, n (%)	26 (51)	21 (70)	165 (62)	0.20
Previous CAD, n (%)	28 (54)	15 (50)	153 (58)	0.66
Chronic kidney disease, n (%)	20 (43)	13 (50)	142 (55)	0.28
Stroke/TIA, n (%)	7 (16)	6 (23)	32 (14)	0.42
DM, n (%)	18 (37)	15 (48)	101 (39)	0.54
COPD/asthma, n (%)	7 (14)	3 (11)	42 (17)	0.71
Laboratory data				
N-terminal proBNP (pg/mL)	4113 (2495–7980)	3634 (2772–6372)	6093 (3646–11 958)	0.003 (b, c)
Troponin I (pg/mL)	0.04 (0.02–0.10)	0.05 (0.02–0.11)	0.04 (0.02–0.09)	0.53
Creatinine (mg/dL)	1.10 (0.90–1.34)	1.23 (0.95–1.71)	1.23 (1.02–1.52)	0.07
eGFR (mL/min/ 1.73 m ²)	61 (48–76)	56 (39–74)	56 (42–70)	0.24
Urea (mg/dL)	42 (32–56)	50 (38–70)	54 (40–77)	0.005 (c)
Sodium (mEq/L)	139 (137–141)	140 (135–142)	139 (136–142)	0.79
Glucose (mg/dL)	131 (103–173)	121 (97–147)	117 (102–139)	0.27
AST (IU/L)	26 (21–36)	28 (22–37)	27 (20–39)	0.81
ALT (IU/L)	34 (21–47)	27 (16–33)	28 (18–48)	0.36
Bilirubin (mg/dL)	0.81 (0.64–1.14)	1.26 (0.87–1.91)	1.20 (0.76–1.79)	0.0004 (a, c)
WBC (G/L)	9.3 (7.7–12.8)	7.6 (6.4–8.8)	8.0 (6.5–9.8)	0.001 (a, c)
CRP (mg/L)	9.2 (3.4–15.2)	7.4 (3.4–15.4)	7.4 (4.0–18.6)	0.93
Haemoglobin (g/dL)	13.9 (12.7–14.7)	13.9 (11.8–14.7)	13.0 (11.6–14.1)	0.001 (c)
Haematocrit (%)	41 ± 4	40 ± 5	39 ± 5	0.01 (c)
GGT (IU/L)	56 (38–89)	73 (36–166)	82 (47–136)	0.03 (c)
Albumin (mg/dL)	3.9 (3.7–4.1)	3.9 (3.6–4.1)	3.7 (3.5–3.9)	0.004 (c)
Acid–base balance in the capillary blood				
pH	7.43 (7.39–7.47)	7.45 (7.43–7.49)	7.45 (7.42–7.48)	0.08
sO ₂	93 (91–95)	94 (90–96)	93 (90–96)	0.88
pO ₂	65 (60–75)	69 (55–78)	66 (58–74)	0.74
pCO ₂	36 (33–42)	34 (30–36)	35 (31–38)	0.01 (a)
HCO ₃ ⁻ standard	24 (23–26)	25 (21–27)	25 (23–27)	0.62
Lactates	2.1 (1.8–2.6)	2.2 (1.6–2.8)	1.9 (1.4–2.4)	0.06
Therapies during hospitalization				
Loop diuretics, i.v., n (%)	50 (96)	31 (100)	266 (99)	0.13
Vasodilator, n (%)	26 (51)	13 (42)	127 (47)	0.73
Inotropes, n (%)	1 (2)	3 (10)	33 (13)	0.09
Beta-blockers, n (%)	50 (96)	29 (94)	257 (96)	0.70
ACE inhibitor/ARB, n (%)	47 (94)	25 (89)	234 (89)	0.52
MRA, n (%)	24 (48)	12 (39)	124 (48)	0.65

ACE, angiotensin-converting enzyme; ALT, alanine transaminase; ARB, angiotensin II receptor blocker; AST, aspartate transaminase; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; i.v., intravenous; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; n, number of patients; TIA, transient ischaemic attack; WBC, white blood cell.

Results are presented as a number of patients (and percentage), mean ± standard deviations, or median (with lower and upper quantile). Legend for statistical analysis between studied groups: a/b/c = $P < 0.05$, where a is comparison between Groups A and B; b is comparison between Groups B and C; and c is comparison between Groups A and C.

cardiac ward. All patients were supervised by cardiologists experienced in HF management. Echocardiography during the first 48 h was performed in 288 (82%) patients—mean left ventricular ejection fraction (LVEF) was $35 \pm 14\%$, and 67% of patients had reduced LVEF (LVEF <40%), 14% mid-range LVEF (LVEF 40–49%), and 19% preserved LVEF (LVEF $\geq 50\%$). With regard to co-morbidities, the most common were arterial hypertension (73% of studied patients), atrial fibrillation (61%), chronic kidney disease (53%), and diabetes mellitus (39%). The mean systolic blood pressure (SBP) on admission was 132 ± 30 mmHg. The median (upper and lower quartiles) plasma concentration of NT-proBNP was 5553 (3253–10 152) pg/mL. During hospitalization, 346 patients (99%) received intravenous loop diuretic, 165 (47%) vasodilators (nitroglycerine, intravenous), 37 (11%) inotropic agents, 335 (96%) beta-blockers, 305 (89%) angiotensin-converting-enzyme or angiotensin II receptor blockers, and 159 (47%) mineralocorticoid receptor antagonists.

According to the described criteria, this population was divided into three groups: A, patients with isolated pulmonary congestion ($n = 52$; 15%); B, patients with isolated peripheral congestion ($n = 31$; 9%); and C, patients with signs of mixed congestion ($n = 269$; 76%).

Clinical characteristics

Clinical characteristics, laboratory findings, and in-hospital treatment are given in *Table 1*. There were no differences in demographics and LVEF on admission to hospital between studied groups. Besides the highest percentage of patients with chronic HF in the group with signs of mixed congestion (56 vs. 58 vs. 74%; $P = 0.006$; Group A vs. B vs. C, respectively), there were no other differences regarding the prevalence of co-morbidities in studied groups.

Laboratory parameters and treatment

Patients with isolated signs of lung congestion (Group A) had lower concentration of urea, bilirubin, and gamma-glutamyl transferase whereas higher level of haematocrit, albumin, and leukocytes (without significant differences in CRP) when compared with patients with peripheral congestion.

The highest NT-proBNP level on admission was observed in Group C [4113 (2495–7980) vs. 3634 (2772–6372) vs. 6093 (3646–11 958) pg/mL; $P = 0.003$; Group A vs. B vs. C, respectively]. No significant differences were observed between studied groups with regard to changes in cardiac biomarkers during the first 48 h of hospitalization (Supporting Information, *Table S1*) and therapies applied during the inpatient care.

Physical findings and acute heart failure signs and symptoms

Table 2 demonstrates physical findings and changes in vital signs and AHF symptoms in studied population.

There were no differences in baseline weight and heart rate. The highest SBP on admission was observed in Group A (145 ± 37 vs. 122 ± 20 vs. 130 ± 29 mmHg; $P = 0.003$; Group A vs. B vs. C, respectively). Patients with isolated lung congestion had also the biggest decrease in SBP and heart rate, with the lowest weight change after 48 h of hospitalization.

In analysed population, 94% of all patients reported dyspnoea at rest, and the mean self-reported severity was 8 (7–10) points using 10-point Likert scale on admission to hospital. Whereas there were no differences between Groups A and C, patients with isolated signs of peripheral congestion had dyspnoea at rest less frequently and with milder magnitude. The shortest duration of dyspnoea before admission was observed in group with isolated lung congestion.

Outcomes

Detailed description of the outcomes in studied population is summarized in *Table 3*.

There were differences in short-term and long-term outcomes, with favourable results in patients with isolated lung congestion. Patients with isolated lung congestion less often experienced in-hospital HF worsening during the first 48 h of hospitalization and stayed in hospital for a shorter period, in comparison with the other groups.

During 1 year of follow-up, 92 (26%) patients died, including 12 (3%) in-hospital deaths. In terms of long-term outcomes, there was a significant difference in 1 year all-cause mortality, with the lowest prevalence in Group A (12 vs. 28 vs. 29%; $P = 0.03$; Group A vs. B vs. C, respectively).

On the univariate analysis, presence of peripheral congestion on admission to hospital in patients with AHF predicted all-cause mortality (*Figure 1*). This association remained significant [hazard ratio (HR) (95% confidence interval, CI): 2.68 (1.06–6.79); $P = 0.04$] after adjusting to other determining variables, which also significantly predicted all-cause mortality: SBP, NT-proBNP, urea, white blood cells, haemoglobin, and albumin (*Table 4*).

Separately, we analysed prognostic role of peripheral congestion in relation to LVEF. As only 14% of patients had HF with mid-range ejection fraction, we combined patients with HF with preserved ejection fraction and HF with mid-range ejection fraction. In patients with HF with reduced ejection fraction, presence of peripheral congestion predicted 1 year all-cause mortality [HR (95% CI): 3.19 (1.07–9.55);

Table 2 Physical findings and changes in vital signs and symptoms in patients with acute heart failure according to signs of congestion on admission

	Changes in physical findings and AHF symptoms			P
	A Isolated signs of lung congestion (n = 52)	B Isolated signs of peripheral congestion (n = 31)	C Signs of lung and peripheral congestion (n = 269)	
Physical findings				
Moderate-severe pulmonary congestion on admission, n (%)	23 (44)	—	78 (29)	<0.0001 (c)
Moderate-severe peripheral oedema on admission, n (%)	—	19 (61)	167 (62)	<0.0001 (b)
Ascites on admission, n (%)	—	5 (16)	47 (17)	0.005 (b)
Elevated JVD on admission, n (%)	—	18 (58)	133 (49)	<0.0001 (b)
Systolic blood pressure on admission (mmHg)	145 ± 37	122 ± 20	130 ± 29	0.003 (a, c)
Change at 24 h	-17 (-48 to -3)	-1 (-10 to 10)	-5 (-21 to 5)	<0.001 (a, c)
Change at 48 h	-22 (-45 to -4)	-2 (-13 to 2)	-10 (-25 to 0)	<0.001 (a, c)
Diastolic blood pressure on admission (mmHg)	84 ± 19	77 ± 11	75 ± 16	0.030 (c)
Change at 24 h	-9 (-20 to 0)	0 (-10 to 3)	-5 (-12 to 0)	0.037 (a)
Change at 48 h	-10 (-20 to 0)	0 (-12 to 1)	-5 (-15 to 1)	0.021 (c)
Heart rate on admission (b.p.m.)	95 (77-110)	80 (68-104)	84 (75-100)	0.121
Change at 24 h	-10 (-32 to -2)	-5 (-14 to 0)	-5 (-18 to 2)	0.036 (c)
Change at 48 h	-16 (-35 to -1.5)	-1 (-10 to 5)	-7 (-20 to 0)	0.006 (a, c)
Weight on admission (kg)	78 ± 18	82 ± 14	82 ± 18	0.42
Change at 24 h	0 (-1.0 to 0)	-1.0 (-2.0 to 0)	-1.0 (-2.0 to -0.3)	0.015 (c)
Change at 48 h	-1.0 (-1.0 to 0)	-2.9 (-3.8 to -0.9)	-2.0 (-3.0 to -1.0)	0.002 (a, c)
Dyspnoea				
Dyspnoea at rest on admission, n (%)	51 (98)	21 (68)	258 (96)	<0.0001 (a, b)
Duration of dyspnoea before admission (days)	1 (1-3)	7 (7-14)	4 (2-7.5)	<0.0001 (a, b, c)
Dyspnoea severity assessed by patient using 10-point Likert scale on admission (points)	8 (7-10)	6 (4-8)	8 (7-10)	0.0004 (a, b)
Difference in dyspnoea severity assessed by patients using 10-point Likert scale after 24 h (points)	-3 (-6 to -2)	-1 (-3 to 0)	-2 (-4 to -1)	0.006 (a)
Difference in dyspnoea severity assessed by patients using 10-point Likert scale after 48 h (points)	-5 (-8 to -2)	-2 (-5 to 0)	-4 (-6 to -2)	0.002 (a, b)

AHF, acute heart failure; JVD, jugular vein distention.

Results are presented as a mean ± standard deviation or median (with lower and upper quantile).

Legend for statistical analysis between studied groups: a/b/c = $P < 0.05$, where a is comparison between Groups A and B; b is comparison between Groups B and C; and c is comparison between Groups A and C.

$P = 0.04$] whereas in those with LVEF $\geq 40\%$, there was no such relationship [HR (95% CI): 1.69 (0.44-6.53); $P = 0.45$], with $P = 0.04$ for significant interaction between the two groups.

Discussion

The main finding of this study is that in patients with AHF, different patterns of congestion detected on physical

Table 3 Clinical outcomes in patients with acute heart failure according to signs of congestion on admission

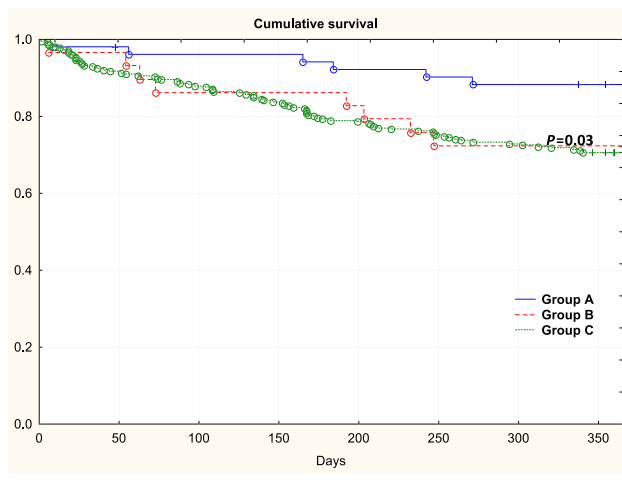
Clinical outcomes	A Isolated signs of lung congestion (n = 52)	B Isolated signs of peripheral congestion (n = 31)	C Signs of lung and peripheral congestion (n = 269)	P
	In-hospital mortality, n (%)	1 (2)	1 (3)	
In-hospital HF worsening during the first 48 h, n (%)	2 (4)	7 (23)	19 (7)	0.006 (a, b)
Duration of index hospitalizations (days)	6 (5-8)	7 (5-11)	7 (6-11)	0.02 (c)
12 months all-cause mortality, n (%)	6 (12)	8 (28)	78 (29)	0.03 (c)

HF, heart failure.

Results are presented as a number of patients (with percentage) or as a median (with lower and upper quantile).

Legend for statistical analysis between studied groups: a/b/c = $P < 0.05$, where a is comparison between Groups A and B; b is comparison between Groups B and C; and c is comparison between Groups A and C.

Figure 1 Kaplan–Meier curves for 1 year all-cause mortality according to the type of congestion on admission to the hospital in patients with acute heart failure.



examination at hospital admission are associated with diverse clinical characteristics, treatment responses, and outcomes.

Until now, many different classifications of AHF based on bedside clinical profiling, history of chronic HF, values of SBP on admission, and presence of co-morbidities have been proposed, which simply reflects clinical diversity of this

population of patients.^{5,6,18,19} Similarly, there are multiple pathophysiologic factors, causing clinical deterioration and leading to development of AHF. Despite such heterogeneity, fluid overload with clinical signs and symptoms of congestion is present in vast majority of patients admitted to hospital due to AHF. It is tempting to expect that characterization of congestion on hospital admission can determine certain clinical phenotypes with subsequent consequences for clinical practice.^{20–23} Therefore, we have decided to characterize patients according to the type of congestion present on physical examination on admission to hospital and evaluate their response to treatment and impact on the outcomes.

Present analysis focuses on patients with clinical signs of congestion on admission who belong to a ‘wet’ profile category, according to recently proposed bedside classification.^{1,6,8} In fact, patients’ characteristics indicate that studied population represents mainly ‘wet–warm’ profile, as majority had preserved SBP and only 11% of patients required inotropic support.

Although the most common physical sign of AHF is peripheral and lung congestion (present as isolated sign or concurrently), only half of patients with decompensation present significant increase in body weight on admission.^{24,25} Fluid overload is a key pathophysiologic feature in AHF, which may manifest as a peripheral, central, or mixed type of congestion.^{1,21,26} Traditionally, it has been established that fluid overload is an equivalent of fluid accumulation caused

Table 4 Predictors of 12 months all-cause mortality in patients with acute heart failure—univariable and multivariable models

Parameters	Univariable models		Multivariable models	
	HR (95% CI)	P	HR (95% CI)	P
Demographics and clinical variables				
Age (years)	1.00 (0.99–1.02)	0.361	—	—
Male (yes)	1.21 (0.72–2.04)	0.453	—	—
LVEF (%)	1.00 (0.98–1.01)	0.787	—	—
SBP (5 mmHg)	0.94 (0.90–0.97)	<0.001	0.94 (0.91–0.98)	0.004
Heart rate (5 b.p.m.)	0.98 (0.94–1.02)	0.297	—	—
Ischaemic HF aetiology (yes)	1.02 (0.67–1.54)	0.927	—	—
Previous CAD (yes)	0.99 (0.65–1.50)	0.946	—	—
Stroke/TIA (yes)	1.54 (0.89–2.67)	0.121	—	—
DM (yes)	1.37 (0.91–2.08)	0.134	—	—
COPD/asthma (yes)	1.17 (0.68–2.01)	0.565	—	—
Laboratory data				
N-terminal proBNP (100 pg/mL)	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.066
Troponin I (pg/mL)	1.71 (0.96–3.03)	0.069	—	—
Urea (mg/dL)	1.01 (1.01–1.01)	<0.001	1.01 (1.00–1.01)	0.016
Glucose (mg/dL)	1.00 (1.00–1.00)	0.658	—	—
WBC (G/L)	1.07 (1.01–1.12)	0.015	1.12 (1.06–1.17)	<0.001
CRP (mg/L)	1.01 (1.00–1.01)	0.071	—	—
Haemoglobin (g/dL)	0.89 (0.79–0.99)	0.031	0.95 (0.84–1.07)	0.363
Albumin (mg/dL)	0.32 (0.20–0.53)	<0.001	0.37 (0.21–0.66)	<0.001
Presence of peripheral congestion (yes)	2.78 (1.21–6.36)	0.016	2.68 (1.06–6.79)	0.037
$\chi^2 = 61$, P for multivariable model <0.0001				

CAD, coronary artery disease; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; DM, diabetes mellitus; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TIA, transient ischaemic attack; WBC, white blood cell.

by either an excessive fluid and salt intake or non-optimal diuretic therapy that lead to an increase of patient's weight. However, this concept made it impossible to explain an underlying pathophysiology of cardiac decompensation in patients with no, or inconsiderable, weight gain and no detectable peripheral oedema. Recently, there is an interest in a new concept of fluid overload in AHF, based on the hypothesis of fluid redistribution.^{26–30} The pathomechanism underlying AHF without noticeable total body weight gain seems to be associated with an endogenous fluid shift from venous body reservoirs, mainly due to the splanchnic bed vasoconstriction triggered by an increased sympathetic activation.^{24,26,31–33}

In our study, majority of patients with AHF had signs of concurrent peripheral and pulmonary congestion (76%), which can suggest mixed pathophysiologic explanation, involving both fluid redistribution and fluid accumulation with mean 2 kg of weight loss after 48 h of diuretic treatment. In patients with isolated pulmonary congestion (15%), a slight weight change during the first 2 days of hospitalization and the highest decrease in SBP and heart rate seem to confirm the hypothesis of fluid redistribution caused by increased sympathetic tone, as the main mechanism of cardiac decompensation in this group of patients. Therefore, patients from Group A may be seen as those with increased left ventricular afterload and significantly elevated SBP, often leading to AHF. Consequently, the target for therapy in this group can be impaired sympathetic/parasympathetic balance, rather than adjustment of diuretic treatment.^{26,31,34} Patients with isolated signs of peripheral congestion had the lowest blood pressure and heart rate on admission and the largest weight loss after 48 h of treatment in comparison with other studied groups—this profile most likely reflects gradual fluid accumulation as the underlying pathophysiology of AHF and can benefit from optimally guided diuretic treatment.³³

Another noticeable observation to emerge from data comparison showed that dyspnoea constituted a common symptom of AHF and was experienced also by 68% of patients without signs of pulmonary congestion. These findings indicate the complexity of dyspnoea pathophysiology and suggest that dyspnoea is not a simple equivalent of lung congestion assessed on physical examination.^{21,35,36} These data are consistent with our previous study, in which we analysed the pattern of dyspnoea onset in AHF, and we have shown that only 26% of patients with dyspnoea at rest, as a major symptom of AHF on admission, presented moderate/severe pulmonary congestion.¹⁷ Our study provides additional interesting finding that the patients with peripheral signs of congestion experienced longer duration of dyspnoea before admission to hospital than patients with pulmonary congestion, in whom dyspnoea onset was more rapid. The aforementioned conclusion also stays in agreement with our previous paper, in which we proved that

patients with subacute onset of dyspnoea (>7 days preceding hospital admission) have poorer short-term and long-term outcomes in comparison with patients with acute onset (≤ 7 days).¹⁷ Almost every third studied patient with AHF manifested as peripheral congestion, either isolated or concurrent with pulmonary congestion, died during 12 months after the index hospitalization. Our study has shown that patients with the involvement of peripheral congestion on admission to the hospital had increased the risk of all-cause death within 1 year by 2.5 times.

In this study, for prognostic purposes, we focused on 1 year all-cause mortality. As congestion type on admission seems to affect in-hospital course, it may also influence risk of post-discharge re-hospitalization for HF. The ESC-EORP-HFA Heart Failure Long-Term Registry included 7865 patients with AHF who were divided into four clinical profiles based on the evidence of congestion and/or hypoperfusion at admission. There were significant differences in the rate of 1 year HF re-hospitalizations between studied groups, with the highest rate observed in those with 'wet-cold' (29%) and 'wet-warm' (26%) profiles compared with 'dry-cold' (17%) and 'dry-warm' (14%) profiles.⁸ Our protocol pre-specified the information for HF hospitalization only for the first cohort (142 patients); thus, this outcome was not analysed in the whole studied population. In the first cohort, however, we did not find any difference regarding re-hospitalization for HF within 1 year between groups (rate of HF hospitalizations: 41 vs. 50 vs. 29%; $P = 0.26$; Group A vs. B vs. C, respectively). However, that results should be interpreted with caution due to small number of patients in studied subgroups in the first cohort.

AHF comprises heterogeneous population of patients in terms of clinical presentation (signs/symptoms, SBP on admission), coexisting co-morbidities, and underlying aetiology of cardiac decompensation. This seems to be one of the possible explanations of recurrent disappointments in clinical trials that apply the rule 'one size fits all' for the inclusion and therapy regardless of different profiles. We believe that our findings can be usefully employed in designing future clinical trials in AHF. The results of this study indicate relevant differences in clinical characteristics, response to standard therapy, and finally, short-term and long-term outcomes between patients with limited central congestion and those with peripheral congestion, the latter group being at higher risk. Therefore, in our opinion, future clinical trials should carefully focus on the aforementioned, particularly vulnerable population of AHF patients with peripheral congestion. It seems that patients with signs of peripheral congestion may benefit from effective decongestive strategies based on new diuretics-like agents or renal replacement therapies. Whereas, patients with isolated lung congestion may rather benefit from new vasodilation agents or therapies targeting sympathetically mediated fluid shift.

Limitations of the study

This study has some limitations. This is retrospective analysis from a single centre combining the data sets from two registries that run during two different time periods. An observational nature of the registries needs to be acknowledged. The classification into three studied groups was determined post hoc. However, we made our best effort to ensure that the primary reason for admission was the AHF. Additionally, we did our best to minimize the chance of the other differential diagnoses to affect the interpretation of the findings of congestion; in all uncertain cases, we confronted them with patients' history, laboratory findings (e.g. levels of NT-proBNP, CRP, and white blood cell), or chest X-ray results. All our patients had markedly elevated NT-proBNP levels [median (interquartile range): 5553 (3189–10 152) pg/mL]; there was no difference in CRP level between studied groups and no difference in prevalence of chronic obstructive pulmonary disease and asthma. Patients with history of severe pulmonary disease and advanced liver or renal disease were excluded from the analysis.

In our study, presence of pleural effusion was not included into the definition of pulmonary congestion. Pleural effusion, although often present in patients hospitalized due to AHF, may either represent sign of central congestion or alternatively result from biventricular failure. In the settings of chronic HF, pleural effusion is predominantly related to left ventricular failure and elevated pulmonary capillary pressure (including capillaries of the visceral pleura) causing fluid to pass into the pleural space. However, concomitant elevation of right atrial pressure by interfering with lymphatic drainage may further increase pleural effusion. Additionally, pleural fluid accumulation due to predominant right ventricular dysfunction is also not rare finding in HF (therefore representing peripheral congestion).

In the setting of AHF, chest X-ray is an important part of the diagnostic work-up to assess pulmonary congestion. However, the idea of this analysis was to focus solely on bedside clinical assessment (without using any other measures), in order to characterize different types of congestion in patients admitted with AHF. Additionally, we did not set up any specific protocol for chest X-ray (to control patients' position, time window from admission, administration of diuretics, etc.), which may lead to potential inconsistencies in the interpretation. Therefore, results of chest X-ray were not included into definition of congestion. Nevertheless, in daily clinical practice, whenever feasible, it is recommended to consider also instrument-based diagnostics tools (such as a chest X-ray and lung and/or abdomen ultrasonography) to improve accuracy of a diagnosis

of peripheral and central congestion based only on bedside physical examination.³³ Dedicated universal protocols for performing and analysis of each diagnostic method are warranted for consistent interpretation of the results in patients with AHF.

Conclusions

In summary, the careful physical examination is a crucial element of a comprehensive assessment of patients admitted to hospital due to AHF. Patterns of congestion in AHF are associated with differences in clinical characteristics, duration of HF symptoms, treatment response, and short-term and long-term outcomes. Therefore, it needs to be considered once designing clinical trials in AHF.

Acknowledgement

J.M.S. is a beneficiary of the Polish National Agency for Academic Exchange (NAWA) in 'The Iwanowska Programme' of medium-term mobility of doctoral students at the Department of Cardiology, University Hospital Zurich, Switzerland.

Conflict of interest

J.M.S., M.S., R.Z., J.B., P.S., S.N.-M., K.S., P.G., W.B., and P.P. report no relationships that could be construed as a conflict of interest.

Funding

This work was supported from the statutory grant no. ST-905 for Department of Heart Diseases, Wrocław Medical University, Poland (Uniwersytet Medyczny im. Piastów Śląskich we Wrocławiu).

Supporting information

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

Table S1. Changes in NT-proBNP and troponin I during the first 48 hours in patients with AHF, according to signs of congestion on admission.

References

- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of. *Eur Heart J* 2016; **37**: 2129–2200.
- Hamo CE, O'Connor C, Metra M, Udelson JE, Gheorghide M, Butler J. A critical appraisal of short-term end points in acute heart failure clinical trials. *J Card Fail* 2018; **24**: 783–792.
- Hamo CE, Butler J, Gheorghide M, Chioncel O. The bumpy road to drug development for acute heart failure. *Eur Heart J Suppl* 2016; **18**: G19–G32.
- ter Maaten JM, Damman K. Down the road from challenges in acute heart failure trials. *Eur J Heart Fail* 2019; **21**: 1423–1425.
- Chapman B, DeVore AD, Mentz RJ, Metra M. Clinical profiles in acute heart failure: an urgent need for a new approach. *ESC Heart Fail* 2019; **6**: 464–474.
- Chioncel O, Mebazaa A, Harjola V-P, 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, ESC Heart Failure Long-Term Registry Investigators. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017; **19**: 1242–1254.
- Javaloyes P, Miró Ò, Gil V, Martín-Sánchez FJ, Jacob J, Herrero P, Takagi K, Alquézar-Arbé A, López Díez MP, Martín E, Bibiano C, Escoda R, Gil C, Fuentes M, Llopis García G, Álvarez Pérez JM, Jerez A, Tost J, Llauger L, Romero R, Garrido JM, Rodríguez-Adrada E, Sánchez C, Rossello X, Parissis J, Mebazaa A, Chioncel O, Llorens P, ICA-SEMES Research Group. Clinical phenotypes of acute heart failure based on signs and symptoms of perfusion and congestion at emergency department presentation and their relationship with patient management and outcomes. *Eur J Heart Fail* 2019; **21**: 1353–1365.
- Chioncel O, Mebazaa A, Maggioni AP, Harjola V, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P, Filippatos G, Ruschitzka F, Seferovic P, Coats AJS, Lund LH, ESC-EORP-HFA Heart Failure Long-Term Registry Investigators. Acute heart failure congestion and perfusion status—impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. *Eur J Heart Fail* 2019; **21**: 1338–1352.
- Punnoose R, Gopal DM, Stevenson LW. Time to update our profiles. *Eur J Heart Fail* 2019; **21**: 1366–1369.
- Palazzuoli A, Ruocco G, Paolillo S, Perrone FP. The use of diuretics in heart failure with congestion: we can't judge a book by its cover. *ESC Heart Fail* 2019; **6**: 1222–1225.
- Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, Stevenson LW. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003; **41**: 1797–1804.
- Thibodeau JT, Drazner MH. The role of the clinical examination in patients with heart failure. *JACC Heart Fail* 2018; **6**: 543–551.
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, ESC Committee for Practice Guidelines (CPG), Vahanian A, Camm J, de Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Böhm M, Corrà U, della Bella P, Elliott PM, Follath F, Gheorghide M, Hasin Y, HERNBERG A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery JL, Verheugt FW, Zamorano JL, Zannad F. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; **29**: 2388–2442.
- McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Pietro MA, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott PP, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur J Heart Fail* 2012; **14**: 803–869.
- Zymliński R, Sokolski M, Siwolowski P, Biegus J, Nawrocka S, Jankowska EA, Todd J, Yerramilli R, Estis J, Banasiak W, Ponikowski P. Elevated troponin I level assessed by a new high-sensitive assay and the risk of poor outcomes in patients with acute heart failure. *Int J Cardiol* 2017; **230**: 646–652.
- Biegus J, Zymliński R, Gajewski P, Sokolski M, Siwolowski P, Sokolska J, Swoboda K, Banasiak M, Banasiak W, Ponikowski P. Persistent hyperlactataemia is related to high rates of in-hospital adverse events and poor outcome in acute heart failure. *Kardiologia Pol* 2019; **77**: 355–362.
- Sokolska JM, Sokolski M, Zymliński R, Biegus J, Siwolowski P, Nawrocka-Millward S, Jankowska EA, Todd J, Banasiak W, Ponikowski P. Patterns of dyspnoea onset in patients with acute heart failure: clinical and prognostic implications. *ESC Heart Fail* 2018; **6**: 16–26.
- Metra M, Felker GM, Zacà V, Bugatti S, Lombardi C, Bettari L, Voors AA, Gheorghide M, Dei CL. Acute heart failure: multiple clinical profiles and mechanisms require tailored therapy. *Int J Cardiol* 2010; **144**: 175–179.
- Ambrosy AP, Gheorghide M. Clinical profiles in acute heart failure: one size fits all or not at all? *Eur J Heart Fail* 2017; **19**: 1255–1257.
- Ferrari R, Bueno H, Chioncel O, Cleland JG, Stough WG, Lettino M, Metra M, Parissis JT, Pinto F, Ponikowski P, Ruschitzka F, Tavazzi L. Acute heart failure: lessons learned, roads ahead. *Eur J Heart Fail* 2018; **20**: 842–850.
- Gheorghide 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**: 423–433.
- Harjola V-P, Mebazaa A, Čelutkienė J, Bettex D, Bueno H, Chioncel O, Crespo-Leiro MG, Falk V, Filippatos G, Gibbs S, Leite-Moreira A, Lassus J, Masip J, Mueller C, Mullens W, Naeije R, Nordegraaf AV, Parissis J, Riley JP, Ristic A, Rosano G, Rudiger A, Ruschitzka F, Seferovic P, Sztarymf B, Vieillard-Baron A, Yilmaz MB, Konstantinides S. Contemporary management of acute right ventricular

- failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016; **18**: 226–241.
23. Krzysztofik J, Ponikowski P. Current and emerging pharmacologic options for the management of patients with chronic and acute decompensated heart failure. *Expert Rev Clin Pharmacol* 2017; **10**: 517–534.
 24. Ponikowski P, Jankowska EA. Pathogenesis and Clinical Presentation of Acute Heart Failure. *Rev Esp Cardiol* 2015; **68**: 331–337.
 25. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM, Robert Wood Johnson Clinical Scholars Program T. Patterns of weight change preceding hospitalization for heart failure. *Circulation* 2007; **116**: 1549–1554.
 26. Cotter G, Metra M, Milo-Cotter O, Dittrich HC, Gheorghiade M. Fluid overload in acute heart failure—redistribution and other mechanisms beyond fluid accumulation. *Eur J Heart Fail* 2008; **10**: 165–169.
 27. Cotter G, Felker GM, Adams KF, Milo-Cotter O, O'Connor CM. The pathophysiology of acute heart failure—is it all about fluid accumulation? *Am Heart J* 2008; **155**: 9–18.
 28. Metra M, Dei Cas L, Bristow MR. The pathophysiology of acute heart failure—it is a lot about fluid accumulation. *Am Heart J* 2008; **155**: 1–5.
 29. Parrinello G, Torres D, Paterna S, di Pasquale P, Licata G. The pathophysiology of acute heart failure: the key role of fluid accumulation. *Am Heart J* 2008; **156**: e19.
 30. Martens P, Mullens W. How to tackle congestion in acute heart failure. *Korean J Intern Med* 2018; **33**: 462–473.
 31. Fallick C, Sobotka PA, Dunlap ME. Sympathetically mediated changes in capacitance. *Circ Heart Fail* 2011; **4**: 669–675.
 32. Burchell AE, Sobotka PA, Hart EC, Nightingale AK, Dunlap ME. Chemohypersensitivity and autonomic modulation of venous capacitance in the pathophysiology of acute decompensated heart failure. *Curr Heart Fail Rep* 2013; **10**: 139–146.
 33. Mullens W, Damman K, Harjola V-P, Mebazaa A, Brunner-La Rocca H-P, Martens P, Testani JM, Tang WHW, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion—a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019; **21**: 137–155.
 34. Gheorghiade M, de Luca L, Fonarow GC, Filippatos G, Metra M, Francis GS. Pathophysiologic targets in the early phase of acute heart failure syndromes. *Am J Cardiol* 2005; **96**: 11G–17G.
 35. Dubé B-P, Agostoni P, Laveneziana P. Exertional dyspnoea in chronic heart failure: the role of the lung and respiratory mechanical factors. *Eur Respir Rev* 2016; **25**: 317–332.
 36. Platz E, Merz A, Silverman M, Lewis E, Groarke JD, Waxman A, Systrom D. Association between lung ultrasound findings and invasive exercise haemodynamics in patients with undifferentiated dyspnoea. *ESC Heart Fail* 2019; **6**: 202–207.