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Clinical determinants and prognostic significance of hypocapnia in acute heart failure

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The aim of this research was to examine the prevalence of hyperventilation (defined by pCO_2 value) among acute heart failure (AHF) patients and to link it with potential triggers and prognosis. All patients underwent dyspnea severity assessment and capillary blood examination on hospital admission and during hospitalization. Out of 241 AHF patients, 57(24%) were assigned to low pCO_2 group ($pCO_2 \leq 30$ mmHg) and 184 (76%) to normal pCO_2 group ($pCO_2 > 30$ mmHg). Low pCO_2 group had significantly lower HCO_3^- (22.3 ± 3.4 vs 24.7 ± 2.9 mmol/L, $p < 0.0001$) and significantly higher lactate level (2.53 ± 1.6 vs 2.14 ± 0.97 mmol/L, $p = 0.03$). No differences between groups were observed in respect to the following potential triggers of hyperventilation: hypoxia (sO_2 92.5 ± 5.2 vs 92 ± 5.6% $p = 0.57$), infection (CRP 10.5[4.9–26.4]vs 7.15[3.45–17.35] mg/L, $p = 0.47$), dyspnea severity (7.8 ± 2.3vs 8.0 ± 2.3 points, $p = 0.59$) and pulmonary congestion (82.5 vs 89.1%, $p = 0.19$), respectively. Low pCO_2 value was related to an increased 4-year all-cause mortality hazard ratio (HR) (95% CI) 2.2 (1.3–3.6); $p = 0.002$ and risk of death and of rehospitalization for HF, HR (95% CI) 2.0 (1.3–3.0); $p = 0.002$. Hyperventilation is relatively frequent in AHF and is related to poor prognosis. Low pCO_2 was not contingent on expected potential triggers of dyspnea but rather on tissue hypoperfusion.

Dyspnea is a fundamental clinical sign in patients hospitalized for acute heart failure (AHF). There are several potential causes of dyspnea that may further lead to hyperventilation in AHF, like: congestion, including pulmonary congestion (promoting hypoxemia), infection, hypoperfusion, hypoxia, activation of hormonal axis (renin–angiotensin–aldosterone), iron deficiency as well as chemoreceptor overactivation. The imbalance in several cardiorespiratory reflex arcs that control and adjust adequate ventilatory and hemodynamic response to changing environmental conditions is a well-known element of heart failure (HF) pathophysiology[1–3]. The increased ventilatory response to hypoxia/hypercapnia mediated by oversensitivity of peripheral chemoreceptors is related to a worse clinical phenotype in chronic HF, including: low exercise tolerance, increased dyspnea sensation as well as high mortality[4–6].

Given the fact, that the carbon dioxide (CO_2) easily diffuses through the capillaries and is readily exchanged at the pulmonary alveolus level, it may serve as a valid indicator of the ventilatory effort with hypocapnia being a marker of hyperventilation.

The data quantifying ventilatory response and hypocapnia in AHF settings is limited. The prognostic significance of hypocapnia among AHF patients has been shown before. However, little is known regarding dynamics of changes in partial pressure of carbon dioxide (pCO_2) during the hospital stay and clinical determinants of hyperventilation (and hypocapnia) in the settings of AHF.

Materials and methods

Study population. This is a single-centre, observational study. The study population included patients admitted with AHF to the Centre of Heart Diseases. 4th Military Hospital, Wroclaw, Poland. All participants were enrolled in the AHF registry carried out between January 2016 and September 2017.

The inclusion criteria were as follows: adult age (≥ 18 years old), AHF as a primary cause of hospitalization, administration of intravenous furosemide at admission and a written informed consent provided by the patient.

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Exclusion criteria were: cardiogenic shock, diagnosis of acute coronary syndrome, known severe liver disease, end-stage renal disease requiring renal replacement therapy.

AHF was defined according to the criteria of the European Society of Cardiology [ESC] guidelines.

Written informed consent was obtained from all patients. This study was approved by local ethics committee (Komisja Bioetyczna. Wroclaw Medical University) and performed in accordance with Declaration of Helsinki and Good Clinical Practice.

Study design. Following admission to hospital clinical examination and detailed information related to subject's demographics (including history of HF), comorbidities, previous treatment and findings obtained from physical examination were recorded. Assessment of dyspnea severity was performed with the use of a self-reported 10-point Likert scale (where 0 corresponds to "absence of dyspnea" and 10 corresponds to "dyspnea of the worst severity/maximal dyspnea").

Venous blood collection, capillary blood gas analyses and assessment of the clinical status were carried out at baseline and at the following subsequent timepoints: day-1 and discharge. The samples were collected, centrifuged and frozen (at – 70 °C) for additional analysis.

Laboratory measurements in peripheral blood. The following laboratory parameters were measured using standard methods in our laboratory:

- blood gas analysis was performed with the use of capillary blood from finger at a baseline and at the following subsequent timepoints: day-1 and discharge. A specimen was analysed with the use of automated blood gas analyser in the hospital's laboratory (ABL FLEX, Radiometer).
- plasma NTproBNP (N-Terminal Pro-B-Type Natriuretic Peptide) (method: immunoenzymatic, Siemens, Marburg, Germany); plasma cardiac troponin (TNI) (method: immunoenzymatic, single Dimension RxL-Max, Siemens)

The following parameters were measured from initially frozen samples:

- markers of inflammation: Interleukin (IL)-6 and interleukin (IL)-22 measured with the use of The Quantikine ELISA Immunoassay kit (R&D Systems. Inc., Minneapolis. MN. USA)
- serum sTfR (mg/L) immunonephelometric technique (Siemens Healthcare Diagnostics. Inc., Deerfield, IL, USA).
- RAAS (renin and aldosterone system) activation method: chemiluminescent immunoassay-CLIS, LIASON.

The chest X-rays results have been reviewed and radiological assessment of pulmonary congestion has been classified as follows: (1) no radiological sings of congestion; (2) radiological sings of congestion (pleural effusion, any signs of congestion not classified as radiological signs of pulmonary edema); (3) radiological signs of severe pulmonary congestion.

On the basis of a current literature review, potential triggers of hyperventilation were identified and investigated. The selected triggers comprised: anaemia (expressed by: haemoglobin, haematocrit). hypoxia (expressed by: partial pressure of O_2 (pO_2), oxygen saturation (sO_2)), infection (represented by: white blood cell count, C-reactive protein), hypoperfusion (systolic blood pressure, pH, lactates), sensation of dyspnea at admission (measured by predefined scale), congestion (presence of pulmonary congestion at admission, NTproBNP), iron deficiency (expressed by ferritin, sfTR (solube transferrin receptor)) and RAAS activation (measured by renin and aldosterone serum concentration).

Categorization. Value of pCO_2 was used as a representation of ventilatory status of the patient. The pCO_2 cut-off on admission was set up at 30 mmHg, upon this value patients were divided to either low pCO_2 group ($pCO_2 \leq 30$ mmHg) or to normal pCO_2 group ($pCO_2 > 30$ mmHg). The cut-off value used to identify low pCO_2 group was established arbitrary with reference to the literature[7–9].

The following signs of HF were examined: (1) oedema (with the use of 0–3-point scale, where 3 corresponds to most severe oedema). (2) pulmonary congestion (with the use of 0–3-point scale, where 3 corresponds to congestion reaching upper parts of lungs) and (3) jugular venous pressure (JVP).

Study outcomes. The clinical endpoints of the study were:

1. In-hospital mortality;
2. One-year all-cause mortality;
3. Composite endpoint of 1-year all-cause mortality and rehospitalization for the HF.

Clinical follow-up. Discharged patients were monitored according to the HF clinic surveillance protocols for at least 1 year. Several sources were used to collect subsequent data regarding patients rehospitalization and survival status, including: patients' testimony, relatives (phone-based interviews), relevant clinic database and/or national register of citizens. Not a single patient was lost to follow-up.

Statistical analysis. Continuous variables with a normal distribution were presented as mean ± standard deviation, variables with skewed distribution were described by medians with [upper and lower quartiles], categorized variables were indicated as numbers and percentages. Statistical analysis between study groups were conducted with the use of T-test, Mann–Whitney U-test or χ^2. The Cox proportional hazards models were utilized to calculate the hazard ratio (HR) with corresponding 95% confidence interval (95% CI) for all-cause mortality. Multivariable analysis was adjusted for confounding variables: age, left ventricular ejection fraction (LVEF), systolic blood pressure at admission, hemoglobin, NTproBNP and blood urea nitrogen. Kaplan–Meier survival curves were used for visualization of survival analysis.

The p value of < 0.05 was considered to be statistically significant. STATISTICA 13 (StatSoft) was utilized to perform statistical analysis.

Results

Baseline characteristics. The study population included 241 AHF patients. predominantly male (72%), with a mean age of 70 ± 13 years. The mean systolic/diastolic blood pressure and heart rate at admission were: 134 ± 32/79 ± 16 mmHg and 90 ± 24 beats per minute, respectively. The mean LVEF was: 39.5 ± 15% with a predominant ischemic etiology (n = 122, 51%). The median of NTproBNP and plasma Troponin I on admission were 5.659 [3.368–11.920] pg/mL and 0.06 [0.03–0.16] ng/mL, respectively. The mean degree of dyspnea reported by the patient on admission was 7.9 ± 2.3 points.

The mean: pH, pO_2, pCO_2, HCO_3^- were 7.43 ± 0.07, 69.33 ± 19.86 mmHg, 35.17 ± 6.68 mmHg and 23.04 ± 3.61 mmol/L, respectively. Table 1 represents detailed information regarding patients' baseline characteristics.

Prevalence of hypocapnia during hospitalization for AHF. There were 57 (24%) patients classified as low pCO_2 and 184 (76%) classified as normal pCO_2. The percentage of patients with low pCO_2 was 23.7% on admission 7.9% at day-1 and 5.0% at discharge (Fig. 1).

Comparison of patients with low vs normal pCO_2 on admission. The low pCO_2 group had significantly lower systolic blood pressure (123 ± 27 vs 137 ± 32 mmHg, p = 0.004) significantly higher lactate (2.53 ± 1.6 vs 2.14 ± 0.97 mmol/L, p = 0.03) and lower HCO_3^- (22.3 ± 3.4 vs 24.9 ± 2.9 mmol/L, p < 0.0001) at baseline. Moreover, the low pCO_2 group had significantly higher levels of NTproBNP 7.493 [5016–16395] vs 5.202 [3068–10152] pg/mL, p = 0.004.

There were no differences between the studied groups in respect to the following potential triggers of hyperventilation: anaemia (e.g., haemoglobin 13.36 ± 2 vs 13.25 ± 2 mg/dL, p = 0.72), hypoxemia (sO_2 92.5 ± 5.2 vs 92 ± 5.6%, p = 0.57), infection status (e.g., CRP 10.5 [4.9–26.4] vs 7.15 [3.45–17.35] mg/L, p = 0.47; IL-6 9.7 [0.5–20.9] vs 8.3 [1.0–21.4] pg/mL, p = 0.93;

IL-22 7.0 [2.0–25.0] vs 6.5 [0.0–18.5] pg/mL, p = 0.18); severity of dyspnea (7.8 ± 2.3 vs 8.0 ± 2.3 points, p = 0.59) and presence of pulmonary congestion (82 vs 89.1%, p = 0.19), respectively. Moreover, there were no differences in RAAS activity and iron status between the groups. The differences between selected, potential determinants of hyperventilation are shown in Table 2.

Comparison of patients with low vs normal pCO_2 at discharge. Patients with low pCO_2 (< 30 mmHg) at discharge had significantly lower HCO_3^- (20.6 ± 1.7 vs 23.3 ± 3.5 mmol/L, p < 0.05) and higher NTproBNP (6953 [2977–11859] vs 3029 [1830–6282] pg/mL, p < 0.05), while there was no difference in systolic blood pressure when compared to the rest of the population. There was a significant correlation between discharge pCO_2 and: discharge NTproBNP R-Spearman correlation coefficient: − 0.15 and discharge lactate: − 0.14, both p < 0.05.

Dyspnea and its change during hospitalization. Patients with low vs normal pCO_2 reported comparable level of dyspnea sensation on admission (7.83 ± 2.3 vs 8.03 ± 2.3 points), day-1 (5.98 ± 2.3 vs 5.28 ± 2.3 points) and at discharge (2.86 ± 2.3 vs 2.24 ± 2.3 points); all p > 0.05. Patients from both groups experienced an improvement at day-1 (vs admission) (p < 0.05). As presented in Fig. 2 the improvement in group A and group B was of similar magnitude (all p > 0.05).

Clinical and laboratory associations of hyperventilation on admission. The correlates of pCO_2 are presented in Table 3. The pCO_2 was independently associated with renin, oxygen saturation and HCO_3^-, with standardized regression coefficients: 0.15, 2.63, -2.22, respectively, all p < 0.05.

Prognostic significance of hyperventilation on admission. The in-hospital mortality was 4.1% (10 events), with a 1-year mortality of 29% (69 events). There was significantly higher proportion of patients who died during hospitalization in the low pCO_2 group 8 (14%) when compared to the rest of the population 2 (1%). p < 0.0001. The pCO_2 expressed as a continuous variable did not impact the 1-year outcomes. However, the low pCO_2 group had significantly worse outcomes even after adjustments for well-defined prognosticators.

Low pCO_2 group as shown in Table 4 was associated with an increased 1-year all-cause mortality hazard ratio (HR) (95% CI) 2.2 (1.3–3.6); p = 0.002 and an increased risk of death and rehospitalization for HF (HR) (95% CI) 2.0 (1.3–3.0); p = 0.002. The Kaplan–Meier curves present the differences in mortality, based on pCO_2 level groups (Fig. 3a,b).

Parameter	All patients
Number of patients	241 (100%)
Gender (male)	174 (72%)
Age (years)	70 ± 12.7
Heart rate (beat/min)	90 ± 24
Systolic blood pressure (mmHg)	134 ± 32
Diastolic blood pressure (mmHg)	79 ± 16
Left ventricle ejection fraction (%)	39.5 ± 14.9
Acute heart failure *(de novo)*	97 (40%)
Heart failure etiology	
Ischemic	122 (51%)
Clinical assessment of pulmonary congestion	
No congestion	30 (12.4%)
< 1/3 pulmonary area	131 (54.4%)
1/3–2/3 pulmonary area	58 (24.1%)
> 2/3 pulmonary area	22 (9.1%)
Radiological assessment of pulmonary congestion*	
No radiological sings of congestion	51 (22%)
Radiological sings of congestion**	173 (73%)
Radiological signs of severe pulmonary congestion	37 (16%)
Ventilation support	
Non-invasive ventilation (yes)	17 (7,1%)
Intubation (yes)	4 (1,66%)
Pleural paracentesis during hospitalization (yes)	13 (5,4%)
Patient's reported dyspnea on admission (points)	7.98 ± 2.31
Blood count	
Haemoglobin (g/dL)	13.3 ± 2.0
Haematocrit (%)	40 ± 5.6
White blood cells (g/L)	9.2 ± 4.4
Platelets (g/L)	208.7 ± 85.9
Components of gas blood test	
pH (potential hydrogen)	7.43 ± 0.07
pCO_2 (partial pressure of carbon dioxide) (mmHg)	35.17 ± 6.68
pO_2 (partial pressure of oxygen) (mmHg)	69.33 ± 19.86
SO_2 (oxygen saturation) (%)	92.11 ± 5.47
HCO_3^- (bicarbonates) (mmol/L)	23.04 ± 3.61
Lactates (mmol/L)	2.23 ± 1.16
C-reactive protein (mg/L)	7.7 [4.2–18.9]
Serum Na^+ (mmol/L)	139 ± 4.4
Serum K^+ (mmol/L)	4.23 ± 0.65
Creatinine (mg/dL)	1.36 ± 0.52
Urea (mg/dL)	59.5 ± 31.47
NTproBNP (pg/mL)	5659 [3368 – 11920]
Troponin I (ng/mL)	0.06 [0.03–0.16]
Total bilirubin (mg/dL)	1.03 [0.72–1.71]
Direct bilirubin (mg/dL)	0.5 [0.37–0.77]
Alanine transaminase (U/L)	31 [21 – 56]
Aspartate transaminase (U/L)	28 [22 – 41]
Albumin (g/dL)	3.78 ± 0.4

Table 1. Baseline characteristics. *Data available in n = 237. **Defined as pleural effusion, any signs of congestion not classified as radiological signs of pulmonary edema.

Discussion

The broad implication of our study is that patients with heart failure and comorbid hypocapnia have worse long-term prognosis and poor clinical outcome.

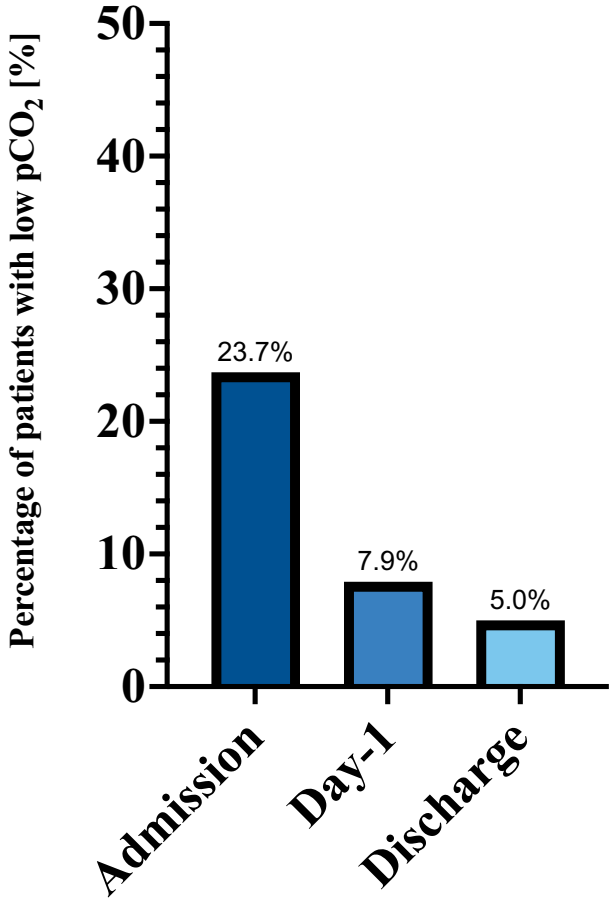

Figure 1. The prevalence of low pCO_2 (≤ 30 mmHg) in AHF patients during hospital stay.

Importantly, we have shown that low pCO_2 was not associated with conventional clinical and laboratory triggers. The results presented here suggest that hypoperfusion was a key factor in the development of hypocapnia.

Dyspnea is the most common symptom among patients with HF and tends to be inevitably more severe as the disease progresses. The term itself refers to the subjective experience of breathing discomfort and is frequently described by patients as an inability to take a deep breath or a chest tightness. This symptom is complex in its etiology as there is a wide spectrum of pathophysiological triggers and mechanisms (cardiac/metabolic/neurogenic/pulmonary/haematological) involved in its development. Even though this phenomenon is widely studied, the diagnostic accuracy of dyspnea assessment seems to be limited due to lack of objective measures. The dyspnea in AHF might be related to hyperventilation (expressed by an increase in tidal volume and/or respiratory rate), but it may also be dependent on the subjective perception of unsatisfied inspiration caused by respiratory muscle weakness or dynamic lung hyperinflation[10]. Clinicians seldom precisely assess the specific physiological variables like respiratory rate, tidal volume or the minute ventilation in AHF patients. Therefore, there is a persistent unmet need for an objective identification of the patient's ventilatory status. A growing body of evidence suggests that hyperventilation may contribute to the development of physiological derangements that result in HF progression[11–14].

Here, we used pCO_2 as surrogate of hyperventilation. We believe that the results of this study provide an insight into heart failure pathophysiology, relations of low pCO_2 with potential clinical triggers of hyperventilation and prognostic significance of hypocapnia in AHF.

First, the results of our study reveal that there were discrepancies between pCO_2 level/hyperventilation and patient self-reported dyspnea. The level of pCO_2 did not affect the sensation of dyspnea reported by AHF patients. Therefore, it can be assumed that subjective dyspnea measures have inadequate diagnostic accuracy for identification of patients with disturbed breathing patterns and pCO_2 seems to be more reliable indicator for detecting hyperventilation.

Second, hyperventilation was not contingent on evident and expected potential triggers such as anaemia (expressed by haemoglobin, haematocrit), infection (expressed by WBC, CRP, IL-6, IL-22), hypoxemia (expressed by pO_2 and sO_2) or pulmonary congestion on physical examination. However, hyperventilating patients had some markers of more advanced disease phenotypes and more severe multi-organ dysfunction. On the other hand, alternative markers of disease progression such as RAAS, iron status or spot urine sodium were comparable between the two groups.

Parameter	pCO_2 partial pressure group		p
	≤ 30 mmHg n = 57 (24%)	> 30 mmHg n = 184 (76%)	
History of pulmonary disease	5 (8.8%)	22 (12%)	0.49
History of thyroid disease	9 (16%)	26 (14%)	0.75
Anaemia			
Haemoglobin (g/dL)	13.36 ± 2	13.25 ± 2	0.72
Haematocrit (%)	40 ± 5.8	40.1 ± 5.5	0.81
Hypoxemia			
pO_2 (mmHg)	69.2 ± 13.1	69.4 ± 21.7	0.94
sO_2 (%)	92.5 ± 5.2	92 ± 5.6	0.57
Infection			
White blood cells (G/L)	9.5 ± 5.1	9.0 ± 4.2	0.49
C-reactive protein (mg/L)	10.5 [4.9–26.4]	7.15 [3.45–17.35]	0.47
IL-6 (pg/mL)	9.7 [0.5–20.9]	8.3 [1.0–21.4]	0.93
IL-22 (pg/mL)	7.0 [2.0–25.0]	6.5 [0.0–18.5]	0.18
Hypoperfusion/hypoxia			
Systolic blood pressure (mmHg)	123 ± 27	137 ± 32	0.004
pH	7.46 ± 0.06	7.43 ± 0.07	0.005
HCO_3^- (mmol/L)	22.3 ± 3.4	24.7 ± 2.9	< 0.0001
Lactates (mmol/L)	2.53 ± 1.6	2.14 ± 0.97	0.03
Dyspnea at admission			
Dyspnea at admission (points)	7.8 ± 2.3	8.0 ± 2.3	0.59
Congestion			
Clinical assessment of pulmonary congestion at admission (yes)	47 (82.5%)	164 (89.1%)	0.19
Radiological assessment of pulmonary congestion*			
No radiological sings of congestion	11 (20%)	40 (22%)	0.75
Radiological sings of congestion**	42 (76%)	131 (72%)	0.52
Radiological signs of severe pulmonary congestion	5 (9%)	32 (17%)	0.12
NTproBNP (pg/mL)	7492.5 [5015.5–16,394.5]	5201.5 [3068–10152]	0.004
Ventilation support			
Non-invasive ventilation (yes)	1 (2%)	16 (9%)	0.07
Intubation (yes)	1 (2%)	3 (2%)	0.94
Pleural paracentesis during hospitalization(yes)	2 (4%)	11 (6%)	0.49
Iron status			
Fe (g/dL)	55.7 ± 27.3	56.4 ± 30.5	0.89
Total iron binding capacity (g/dL)	349.6 ± 58	346.2 ± 73.1	0.76
sTfR at admission (mg/L)	2.2 ± 0.7	1.9 ± 0.9	0.07
Ferritin (g/L)	105.0 [81.0–219.0]	154.5 [83.5–247.5]	0.16
RAAS activation			
Renin (μIU/mL)	33.5 [4.2–262.3]	27.7 [6.8–96.6]	0.52
Aldosterone (ng/dL)	12.5 [6.9–29.6]	10.5 [6.5–15.7]	0.17
Organ dysfunction			
Serum Na^+ (mmol/L)	136.5 ± 5.15	139.7 ± 3.8	0.0
Serum K^+ (mmol/L)	4.34 ± 0.7	4.2 ± 0.6	0.13
Creatinine (mg/dL)	1.48 ± 0.6	1.32 ± 0.5	0.04
Spot urine sodium at admission (mmol/L)	80 ± 35	89 ± 35	0.13
Spot urine sodium at day-1 (mmol/L)	74 ± 34	76 ± 40	0.66
Urea (mg/dL)	68.7 ± 39	56.7 ± 28	0.02
Troponin I (ng/mL)	0.06 [0.03–0.11]	0.06 [0.03–0.2]	0.6
Total bilirubin (mg/dL)	1.6 [0.9–2.2]	0.9 [0.7–1.5]	0.02
Direct bilirubin (mg/dL)	0.7 [0.5–1]	0.48 [0.34–0.7]	0.03
Alanine transaminase (U/L)	37 [22–70.5]	30 [21–50]	0.01
Aspartate transaminase (U/L)	30.5 [24.5–64]	28 [20–40]	0.02
Albumin (g/dL)	3.72 ± 0.34	3.8 ± 0.4	0.22

Table 2. Comparison of selected, potential triggers of hyperventilation by pCO_2 level on admission. *Data available in n = 237. **Defined as pleural effusion, any signs of congestion not classified as radiological signs of pulmonary edema.

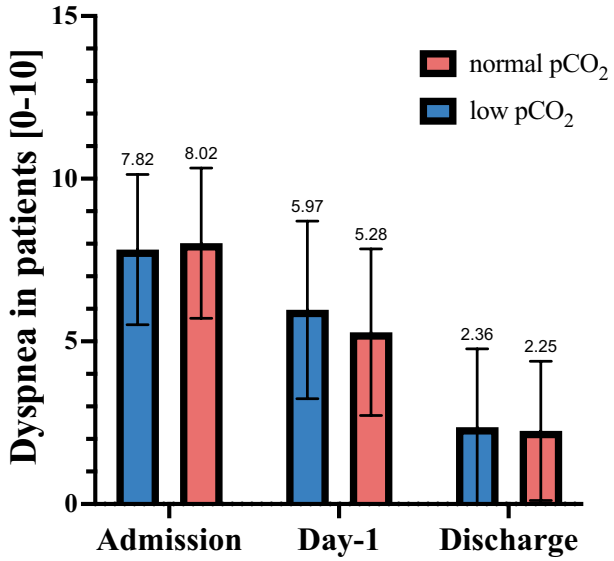

Figure 2. Comparison of dyspnea perception between patient with different pCO_2 level. Assessment of dyspnea perception was performed with the use of a self-reported 10-point Likert scale. Red—patients with normal pCO_2 (> 30 mmHg). Blue—patients with low pCO_2 (≤ 30 mmHg).

Variable	Univariable		Multivariable (intercept = 0)	
	Pearson correlation coefficient	p	Standardized regression coefficient*	p
sfTR (mg/L)	− 0.18	0.02		
Renin (μIU/mL)	− 0.18	0.01	0.15	< 0.05
Hemoglobin (g/dL)	− 0.05	0.53		
pO_2 (mmHg)	0.02	0.76		
sO_2 (%)	− 0.22	< 0.01	2.63	< 0.01
CRP (mg/L)	− 0.04	0.57		
HCO_3^- (mmol/L)	0.14	0.06	− 2.22	< 0.01
Lactate (mmol/L)	0.04	0.58		
Dyspnea (points)	0.14	0.06		
Systolic blood pressure (mmHg)	0.35	0.00		
NT-proBNP at admission (pg/mL)	− 0.18	0.02		
Aldosterone (ng/dL)	− 0.29	< 0.01		

Table 3. Clinical and laboratory determinants of hyperventilation ($pCO_2 \leq 30$ mmHg on admission). *sFTR* soluble transferrin receptor, *pO_2* partial pressure of oxygen, *sO_2* oxygen saturation, *CRP* C-reactive protein, *HCO_3^-* bicarbonate, *NT-proBNP* N-terminal prohormone of brain natriuretic peptide. *Progressive stepwise regression model – only final statistically significant variables of the model are presented.

	HR (95% CI) Univariate model	HR (95% CI) Multivariable model*
360-day all-cause morality		
pCO_2 (mmHg)	0.97 (0.9–1.0); p = 0.33	
Low pCO_2 group	2.2 (1.3–3.6); p = 0.002	1.8 (1.1–3.0) p < 0.01
360-day all-cause mortality or rehospitalization for heart failure		
pCO_2 (mmHg)	0.97 (0.9–1.0); p = 0.25	
Low pCO_2 group	2.0 (1.3–3.0); p = 0.002	1.6 (1.04–2.59); p < 0.05

Table 4. One-year all-cause mortality and heart failure rehospitalizations risks in relation to pCO_2 level on admission. *Adjusted for: age, ejection fraction, systolic blood pressure at admission, haemoglobin. NTproBNP and serum creatinine.

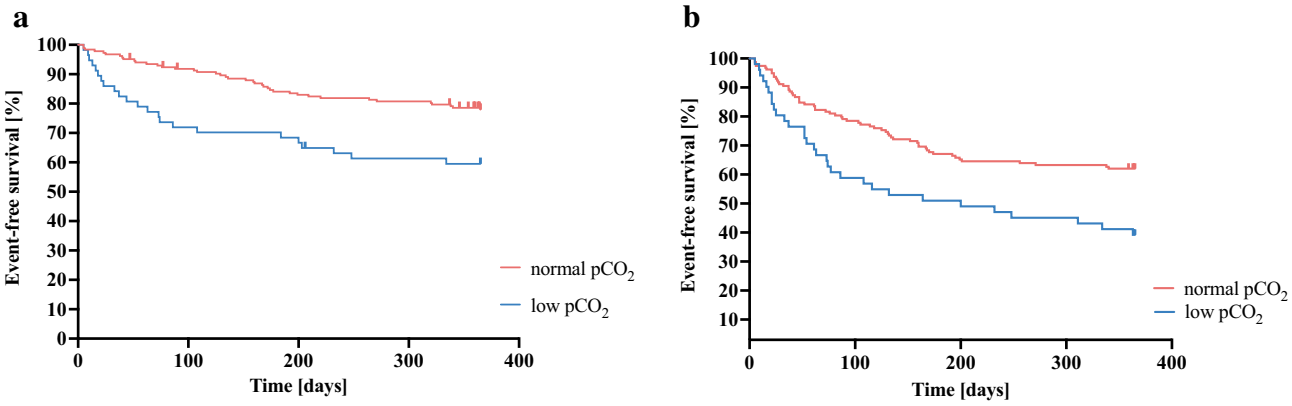

Figure 3. Kaplan–Maier curves for death or heart failure rehospitalization (whichever occurred first) by pCO_2 level on admission. (**a**) Death analysis. Log rank p = 0.002. Red line—patients with normal pCO_2 value (> 30 mmHg). Blue line—patients with low pCO_2 value (≤ 30 mmHg). (**b**) Death or heart failure rehospitalization (whichever occurred first) by pCO_2 level on admission. Log-rank p = 0.002. Red line—patients with normal pCO_2 value (> 30 mmHg). Blue line—patients with low pCO_2 value (≤ 30 mmHg).

Both groups differed in relation to markers of hypoperfusion and hypoxemia/hypoxia. A higher lactate level on admission was observed in the group with low pCO_2. Lactate as a product of an anaerobic metabolism corresponds to impaired tissue perfusion. In response to energetic stress (as during AHF episode) energy demand increases and the sympathetic nervous system hyperactivates, all of which result in an increased glycolysis and lactate accumulation. Under conditions of insufficient tissue perfusion, persistent energy debt exceeds the buffering capacity of the body what consecutively leads to the development of hyperlacticaemia and metabolic acidosis. This goes also with agreement with the occurrence of metabolic acidosis (the lower bicarbonate levels) observed in the hyperventilating group. The metabolic acidosis may also be a surrogate of inadequate peripheral perfusion in AHF. As a result of bicarbonate depletion, ventilatory compensation (in the form of hyperventilation) emerges to maintain acid–base balance.

Therefore, it can be inferred that one of the mechanisms underlying hypocapnia in AHF is related to response to peripheral hypoperfusion. Thus, we may speculate that hypoperfusion (rather than direct hypoxemia) contributed to hyperventilation in an attempt to buffer the developing acidosis at the expense of CO_2 loss. On the other hand, renin was independently related to hyperventilation, which may indicate that patients with more advanced stages of the disease (defined by elevated renin) as well as those with more severe metabolic collapse on admission to the hospital are more likely to develop hyperventilation.

As elegantly shown by Torres-Torrelo et al. peripheral chemoreceptors are also lactate sensors[15]. Thus, overactivation of the chemoreflex arc may be seen as hypothetical link between diminished tissue perfusion and increased ventilatory effort resulting in hypocapnia. It is also worth noting that HF individuals with hypersensitive peripheral chemoreceptors (~ 30% of HF patients) are characterized by worse prognosis. Therefore, it may be speculated that poor outcomes seen in our study in low pCO_2 group might have been partly related to that fact. Assessment of peripheral chemosensitivity would definitely shed more light on the matter.

The association between hemodynamic impairment, enhanced sensitivity to carbon dioxide and Cheyne–Stokes respiration (CSR) among patients with HF is an additional contributing factor that should be taken under consideration[16]. Hyperventilation induced hypocapnia contributes to the ventilatory instability and the development of a periodic breathing with central sleep apnoea (CSA)[16]. Indeed, as it was presented by Naughton et al., patients with CSR-CSA had significantly lower values of pCO_2 in comparison to patients who did not present this breathing pattern[17].

It should be noted that, Cheyne-Stokes ventilation is a marker of a poor prognosis in HF and the central sleep apnoea is related to higher mortality risk in HF population[18]. Consequently, it can be assumed, that this aspect could have partially contributed to the poor clinical outcome observed in a group with hypocapnia. This assumption should be addressed in future studies.

Interestingly, despite clinical improvement 5% of patients had persistent hypocapnia at discharge. We may only speculate that low discharge pCO_2 identifies patients with more profound metabolic misbalance/hypoperfusion that may be imperceptible from clinical perspective, analogically to those patients being discharged with residual congestion[19,20]. This theory may be supported by the fact that discharge pCO_2 correlated with both discharge lactate and NTproBNP. However, we do not have a conclusive evidence that those two populations overlap in our study.

Study limitations. This is a single-centre, observational study, which recruited relatively low number of patients. It should be emphasized that hypocapnia on admission for AHF might not be a simple function of hyperventilation. It is well possible that in some patients it was present even before the acute event. This could potentially be related to chronic renal disease with concomitant metabolic acidosis, the presence of periodic breathing or other unidentified factors—which by themselves may affect the survival. The pCO_2 cut-off value used in our study was set up arbitrary (however in line with literature data), which is also an obvious limitation.

In conclusion, hypocapnia is relatively frequent among patients admitted to the hospital with AHF and related with poor prognosis. Low pCO_2 was not contingent on evident and expected potential clinical and laboratory triggers, while tissue hypoperfusion seemed to play an important role in its' development.

Data availability

The datasets used in the current research are available from the corresponding authors on reasonable request.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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