**Original article**

**Prognostic implications of arterial blood gases in acute decompensated heart failure**

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**Abstract**

Background: The prognostic value of arterial blood gases (ABG) in patients with acute decompensated heart failure (ADHF) is not well-established. We therefore conducted the present study to determine the relationship between ABG on admission and long-term mortality in patients with ADHF.

Methods: We studied 588 patients consecutively admitted to our department with ADHF. ABG and classical prognostic variables were determined at patients’ arrival to the emergency department. The independent association among the main variables of ABG (pO2, pCO2 and pH) and mortality was assessed with Cox regression analysis.

Results: At a median follow-up of 23 months, 221 deaths (37.6%) were registered. 308 (52.4%), 54 (9.2%) and 50 (8.5%) patients showed hypoxemia (pO2<60 mm Hg), hypercapnia (pCO2>50 mm Hg) and acidosis (pH<7.35), respectively. Patients with hypoxemia, hypercapnia and acidosis did not show higher mortality rates (38% vs. 37.1%, 42.6% vs. 37.1%, and 48% vs. 38.6%, respectively; p-value = ns for all comparisons). In multivariate analysis, after adjusting for well-known prognostic covariates, pO2, pCO2 and pH did not show a significant association with mortality. Hazard ratios (HR) for these variables were: pO2, per increase in 10 mm Hg: 0.99 (95% CI: 0.90–1.09), p = 0.861; pCO2, per increase in 10 mm Hg: 1.12 (95% CI: 0.91–1.39), p = 0.262; pH per increase in 0.1: 1.01 (95% CI: 0.99–1.04), p = 0.309. When dichotomizing these variables according to established cut-points, the HR were: hypoxemia (pO2<60 mm Hg): 1.07 (95% CI: 0.81–1.40), p = 0.637; hypercapnia (pCO2>50 mm Hg): 0.98 (95% CI: 0.62–1.57), p = 0.952; acidosis (pH<7.35): 1.38 (95% CI: 0.87–2.19), p = 0.173.

Conclusion: In patients admitted with ADHF, admission arterial pO2, pCO2 and pH were not associated with all-cause long-term mortality.

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**1. Introduction**

Approximately 10% to 15% of all emergency department presentations are due to shortness of breath, mostly secondary to heart failure (HF) or lung disease. The most frequent complaint of patients with acute HF is dyspnea [1,2]. Recently, the European Society of Cardiology (ESC) has proposed a clinical classification of acute HF into five well-established categories. Among them, acute decompensated HF (ADHF), which is the most common presentation in acute HF, was defined as a progressive worsening of a known chronic HF on treatment and evidence of systemic and pulmonary congestion. As expected, dyspnea is the most frequent complaint in patients with ADHF [3].

In patients with acute dyspnea, arterial blood gases (ABG) are one of the main tools for decision making in the emergency department. ABG are a basic tool in the diagnosis work-up for these patients and also for guiding therapy in patients with chronic obstructive pulmonary disease (COPD) exacerbation [4,5], asthma [6], pneumonia [7] or pulmonary embolism [8,9]. However, its prognostic value in patients with ADHF is not well-established. The ESC heart failure guidelines [3] recommend assessing ABG in patients with acute HF, with the rationale that acidosis, due to poor tissue perfusion or CO2 retention is associated with a poor prognosis, especially in those cases with a clinical abrupt-onset presentation, such as acute pulmonary edema, hypertensive emergency or cardiogenic shock. However, we believe this rationale is merely speculative in ADHF, since there is no evidence in the literature that has demonstrated its association with poor prognosis.

The present study was conducted to determine the relationship between the main variables traditionally measured in the ABG sample (pO2, pCO2 and pH) at hospital admission and long-term mortality in patients with ADHF.
2. Methods

2.1. Study population and protocol

We studied a cohort of 1181 patients consecutively admitted in our institution from January 2003 to July 2009, with a diagnosis of acute HF. Following current guidelines [3], diagnosis of acute HF was defined as a rapid onset of symptoms and signs secondary to abnormal cardiac function plus any objective evidence of structural or functional abnormality of heart at rest (cardiomegaly, third heart sound, cardiac murmur, abnormality of the echocardiogram or raised natriuretic peptide levels); as a subtype of acute HF, ADHF was defined as a progressive worsening of a known chronic HF on treatment and evidence of systemic and pulmonary congestion. A trained cardiologist confirmed the diagnosis of ADHF in all patients at hospital arrival. Therefore, we excluded for the present analysis acute HF cases other than ADHF, such as acute pulmonary edema (n = 258), hypertensive acute HF (n = 98), cardiogenic shock (n = 14) and right ventricular HF (n = 7). Among 804 patients with ADHF, 216 were also excluded for the following reasons: 190 (23.6%) because ABG determinations were not available (the physician in charge did not consider it necessary) and 26 (3.2%) because ABG were assessed after starting treatment. Thus, the final study cohort included 588 ADHF patients (see flow chart, Fig. 1).

Demographic information, medical history, vital signs, 12-lead electrocardiogram, laboratory and drug utilization were routinely collected in the emergency department and throughout the hospital course following pre-established registry questionnaires. ABG were measured under stable conditions, dyslipidemia, heart rate on admission, systolic blood pressure on admission, serum creatinine, measured under stable conditions, dyslipidemia, heart rate on admission, systolic blood pressure, left ventricular ejection fraction (LVEF) was assessed with two-dimensional echocardiography in all patients during hospitalization (Agilent Sonos 5500-Phillips).

All patients received intravenous treatment with furosemide at least during the first 48 hours of admission. Treatment with angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), betablockers, aldosterone antagonists, anti-oagulants and other therapeutic strategies was individualized following established guidelines [3].

Patients were followed until death. They were censored, however, by having undergone cardiac transplantation, cardiac valve replacement surgery, or lost to follow-up. All-cause mortality was selected as the main clinical endpoint. Patients’ clinical status and endpoint ascertainment were routinely evaluated by trained cardiologists either during recurrent hospitalizations or outpatient visits.

2.2. Statistical analysis

Continuous variables were expressed as mean (95% CI) or median (interquartile range) as appropriate. Discrete variables were presented as percentages. Baseline characteristics were compared among those patients with and without hypoxemia, hypercapnia and acidosis. All-cause mortality rates were depicted among time using the Kaplan–Meier method, and their differences tested by the Peto-Peto Prentice test. The independent association between each component of the ABG (pO2, pCO2 and pH) and mortality was assessed using the Cox regression analysis.

Candidate covariates for the initial multivariable model were selected based on previous medical knowledge. All variables listed in Table 1 were tested with prognostic purposes. Then, a reduced and parsimonious model was derived by using backward stepdown selection, leading to a final model with the following covariates: gender, age, previous admission for acute HF, last NYHA class measured under stable conditions, dyslipidemia, heart rate on admission, systolic blood pressure on admission, serum creatinine, serum sodium and haemoglobin. The proportionality assumption for the hazard function over time was tested by means of the Schoenfeld residuals. The discrimination and calibration of the model were assessed using the Harrel’s C-statistics and the Grommesy and Borgan test [10] respectively. A 2-sided p-value of <0.05 was considered to be statistically significant for all analyses. All analyses were performed using STATA 11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

3. Results

3.1. Baseline characteristics

The mean age of the study population was 74±11 years; 306 patients (52%) were female, 244 (41.5%) had been previously admitted for acute HF and 317 (53.9%) exhibited left ventricular ejection fraction ≤50%. Three hundred thirty-six (57.1%) patients showed an abnormal ABG analysis, as follows: 308 (52.4%), 54 (9.2%) and 50 (8.5%) patients showed hypoxemia (pO2<60 mm Hg), hypercapnia (pCO2≥50 mm Hg) and acidosis (pH<7.35), respectively. Tables 1, 2 and 3 show the clinical characteristics of the study population according to the presence of hypoxemia, hypercapnia and acidosis, respectively.

Hypoxemia was more frequent among females, those with higher means of age, systolic blood pressure and LVEF and without peripheral edema. Likewise, lower means of serum creatinine and brain natriuretic peptide (BNP) were observed in patients with hypoxemia. Interestingly, no differences in cardiovascular risk factors, etiology or comorbidity were found among patients with or without hypoxemia. Hypercapnia was more prevalent in patients with NYHA class III/IV (last measurement under clinically stable conditions, and before the index admission), females, diabetics, COPD patients and in those with peripheral edema. Likewise, patients with hypercapnia showed higher means of systolic blood pressure, left ventricular ejection fraction and serum sodium and lower means of BNP.

Finally, patients with acidosis showed higher means of systolic blood pressure and serum creatinine and were treated less frequently with spironolactone and ACEI.

3.2. Long-term mortality and arterial blood gases in ADHF

At a median follow-up of 23 months (IQR: 7–43), 221 deaths (37.6%) were registered: 32 occurred during the index hospitalization and 189 after discharge. Crude mortality rates were not different for patients with hypoxemia, hypercapnia or acidosis (38% vs. 37.1%, p = 0.833; 42.6% vs. 37.1%, p = 0.426; and 48% vs. 36.6%, p = 0.112, respectively). Kaplan–Meier curves confirmed that cumulative risk of
show a signiﬁcantly higher discriminative ability of 0.741; the Gronnesby and
Gatsonis C index 

AHF: acute heart failure; NYHA: New York Heart Association; COPD: chronic pulmonary obstructive disease; PAD: peripheral arterial disease; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor antagonist; BNP: brain natriuretic peptide; LVEF: left ventricular ejection fraction; LAD: left atrial diameter; LVDD: left ventricular diastolic diameter.

Values are expressed as mean (95% CI). Categorical variables are presented as percentages.

* Last NYHA functional class measured under clinically stable conditions.

b Presented as median (interquartile range).

death did not differ among patients with hypoxemia, hypercapnia or acidosis (Fig. 2 a, b and c).

In multivariable Cox regression analysis, pO2, pCO2 and pH did not show a significant association with all-cause mortality. Evaluated in a continuous metric, the hazard ratios (HR) for pO2 (per 10 mm Hg), pCO2 (per 10 mm Hg) and pH (per 0.1 scale) were: 0.99 (95% CI: 0.90–1.09), p = 0.861; 1.12 (95% CI: 0.91–1.39), p = 0.262 and; 1.01 (0.99–1.04), p = 0.309, respectively. The Harrell’s C-statistics of the multivariate model that included pO2, pCO2 and pH as continuous showed high discriminative ability of 0.741; the Gronnesby and Borg test of goodness-of-ﬁt showed a good model calibration (p = 0.802).
No significant interactions were found between hypoxemia, hypercapnia and acidosis with any of the most representative subgroups such as being older than 65, female, those with preserved systolic function, ischemic heart disease and previous admission for AHF, by showing not only the lack of significance but a similar direction of the effect.

Because the availability of ABG may be considered a potential surrogate of clinical severity, we tested the prognostic value of having performed an ABG at patients' arrival, but this time using the entire population of patients with ADHF (n=804). The adjusted HR for mortality showed no significant differences between patients with or without ABG measurements [HR: 1.25 (95% CI: 0.92–1.70), p=0.162], a result that diminished the likelihood of significant selection bias in our results.

Similarly, non-significant results were observed by dichotomizing these variables with established cut points. The adjusted HRs for hypoxemia (pO2 ≤ 60 mm Hg), hypercapnia (pCO2 > 50 mm Hg) and acidosis (pH < 7.35) were: 1.07 (95% CI: 0.81–1.40), p = 0.637; 0.98 (95% CI: 0.62–1.57), p = 0.952; and 1.38 (0.87–2.19), p = 0.173, respectively (Fig. 3).

Table 3
Baseline characteristics stratified by the presence of acidoses.

<table>
<thead>
<tr>
<th>pH&lt;7.35</th>
<th>pH≥7.35</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=50 (8.3%)</td>
<td>n=538 (91.5%)</td>
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</table>

Demographic and medical history

<table>
<thead>
<tr>
<th>Variable</th>
<th>n=50 (8.3%)</th>
<th>n=538 (91.5%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>76 (74–79)</td>
<td>73 (72–74)</td>
<td>0.063</td>
</tr>
<tr>
<td>Gender (male), n (%)</td>
<td>21 (42.0)</td>
<td>261 (48.5)</td>
<td>0.377</td>
</tr>
<tr>
<td>Debut AHF, n (%)</td>
<td>33 (66.0)</td>
<td>311 (57.8)</td>
<td>0.256</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
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</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
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<td>220 (40.9)</td>
<td>0.312</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>3 (6.0)</td>
<td>43 (8.0)</td>
<td>0.601</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>21 (42.0)</td>
<td>227 (42.2)</td>
<td>0.679</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>22 (44.0)</td>
<td>183 (34.1)</td>
<td>0.166</td>
</tr>
<tr>
<td>Valvular heart disease, n (%)</td>
<td>9 (18.0)</td>
<td>148 (27.6)</td>
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<tr>
<td>NYHA class III/IV, n (%)a</td>
<td>14 (28.0)</td>
<td>115 (21.4)</td>
<td>0.292</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>17 (34.0)</td>
<td>123 (23.2)</td>
<td>0.088</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>6 (12.0)</td>
<td>55 (10.2)</td>
<td>0.601</td>
</tr>
<tr>
<td>Radiological pleural effusion, n (%)</td>
<td>25 (50.0)</td>
<td>285 (53.0)</td>
<td>0.683</td>
</tr>
<tr>
<td>Peripheral edema, n (%)</td>
<td>9 (18.0)</td>
<td>125 (23.2)</td>
<td>0.387</td>
</tr>
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Effect of acidosis on survival (Fig. 2).

a Last NYHA functional class measured under clinically stable conditions.

b Presented as median (interquartile range).

The adjusted HRs for associations of the most representative variables and some of the most significant cut points are presented in Table 4. For the sake of simplicity, we did not present the results of the remaining variables, which were not significant. The adjusted HRs range from 0.637 to 1.70, with p-values ranging from 0.039 to 0.952.

Similarly, non-significant results were observed by dichotomizing these variables with established cut points. The adjusted HRs for hypoxemia (pO2 < 60 mm Hg), hypercapnia (pCO2 > 50 mm Hg) and acidosis (pH < 7.35) were: 1.07 (95% CI: 0.81–1.40), p = 0.637; 0.98 (95% CI: 0.62–1.57), p = 0.952; and 1.38 (0.87–2.19), p = 0.173, respectively (Fig. 3).
4. Discussion

The present study showed, in a large and non-selected population with ADHF and after a thorough multivariable adjustment, that ABG (pO2, pCO2 and pH) determined at patients’ arrival to the emergency department are not associated with all-cause long-term mortality. We believe that the present results may bring to the notice of the emergency physicians to avoid the routine use of ABG results for prognostic assessment in patients during an ADHF episode.

4.1. ADHF prognosis

Recent ESC heart failure guidelines [3] encourage the use of acute HF classification. ADHF syndrome has become the most prevalent presentation from all acute HF syndromes, with 1-year mortality in most registries about 20–30% [11,12]; these figures frequently exceed the mortality rates observed in other more abrupt dyspneic presentations of acute HF, such as acute pulmonary edema or hypertensive acute HF [13,14]. Thus, it has been recommended to base the initial risk stratification of patients with ADHF on a rigorous clinical, radiologic, electrocardiographic and biomarker evaluation [3]. Based on our results, the addition of ABG results did not provide any additional prognostic utility to the ESC recommendations. Moreover, uniform results were observed in the most important subgroups of patients, such as women, preserved systolic function, previous admissions for AHF and ischemic etiology. In addition, the fact that patients with no ABG (because the physician in charge did not consider them necessary) have similar prognosis as patients with ABG assessment further supports our results.

4.2. Biological interpretation of the present results

In acute HF, lung function disturbances are related to reduction in vital and total lung capacity, lung diffusion capacity and lung compliance. Consequently, resistance to air flow is moderately increased, while total and functional residual volume remain normal [15]. Usually, patients with chronic left ventricular failure exhibited a restrictive ventilatory defect [16,17] characterized by a reduction in vital capacity resulting from the replacement of air in the lungs by blood or interstitial fluid.

Previous studies have shown that lung function abnormalities can be reduced, or even resolved, with different treatments, including ACEI [18–20], ultrafiltration [21,22] and heart transplantation [23,24]. In a classic study, Light et al. [25] evaluated the changes in pulmonary function in 28 patients hospitalized for congestive HF. Initially, patients had both obstructive and restrictive ventilatory dysfunction that rapidly improved with treatment initiation. In another study, Niset et al. [23] evaluated the reversibility of the lung dysfunction in 47 patients with severe chronic congestive HF before and one year after heart transplantation. These authors showed that restrictive ventilatory defect induced by chronic HF was reversible, whereas the exception of the reduction in diffusion lung capacity for carbon monoxide (DLCO) was not improved, which probably reflected permanent changes in the lung vasculature.

In addition, widely used treatments in patients with HF such as ACEI or ARB have been shown to have pleiotropic beneficial effects on lung function [12]. These changes have been mainly attributed to the reduction of levels of angiotensin II at the level of the pulmonary microvasculature and increase exposure to prostaglandins, especially prostacyclin and nitric oxide, as a result of increased local kinin concentrations.

Even considering the limitation of these studies, which include small sample sizes and selected patients, they reinforce the idea that gas exchange disturbances in ADHF are mainly transitory, unlike the dyspnea that is consequence of a primary lung disease. Such reversibility is what made our results relevant. Thus, we speculate that most of patients with ADHF show reversible lung function disturbances that are limited to acute episodes.

4.3. Clinical implications

Due to a lack of evidence linking ABG with long-term mortality, long-term prognosis assessment should not be based on data from admission arterial pO2, pCO2 and pH. As stated by guidelines, a thorough clinical, electrocardiographic, radiologic and biomarker evaluation should be standard medical practice in these patients.

4.4. Strengths and limitations

At present, this is the first study performed in a large and representative population of patients with ADHF, and analyzed with an appropriate methodology, which suggests that the main variables of ABG did not have prognostic implications on long-term mortality.

Some limitations, however, should be addressed. First, determination of BNP and other biomarker-related variables was assessed during patient’s hospitalization and not on patient’s arrival to the emergency department; this fact precludes their use in the multivariable model. Second, due to its observational nature, the possibility of selection bias and/or residual confounding from unknown or unmeasured covariates cannot be excluded. Third, this is a single-center registry which may limit the transportability of our conclusion to other populations. Fourth, having a low sample size in certain subgroups precludes obtaining robust estimates regarding a possible differential effect of ABG in these subgroups.

4.5. Conclusions

In patients with ADHF, admission arterial pO2, pCO2 and pH were not associated with all-cause long-term mortality.

Learning points

- In patients admitted with acute decompensated heart failure, admission arterial pO2, pCO2 and pH are not associated with all-cause long-term mortality.
- Due to a lack of evidence linking ABG with long-term mortality, long-term prognosis assessment should not be based on data from admission arterial pO2, pCO2 and pH. As stated by guidelines, a thorough clinical, electrocardiographic, radiologic and biomarker evaluation should be standard medical practice in these patients.

Conflict of interest

None to declare.
References


[3] European Society of Cardiology; Heart Failure Association of the ESC (HFA); European Society of Intensive Care Medicine (ESICM). BTS guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008;10:933–89.


