Respiratory failure and bioelectrical phase angle are independent predictors for long-term survival in acute heart failure

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ABSTRACT

Background. The assessment of long-term mortality in acute decompensated heart failure (ADHF) is challenging. Respiratory failure and congestion play a fundamental role in risk stratification of ADHF patients. The aim of this study was to investigate the impact of arterial blood gases (ABG) and congestion on long-term mortality in patients with ADHF. Methods and results. We enrolled 252 patients with ADHF. Brain natriuretic peptide (BNP), blood urea nitrogen (BUN), phase angle as assessed by means of bioimpedance vector analysis, and ABG analysis were collected at admission. The endpoint was all-cause mortality. At a median follow-up of 447 d (interquartile range [IQR]: 248–667), 72 patients died 1–840 d (median 106, IQR: 29–233) after discharge. Respiratory failure types I and II were observed in 78 (19%) and 53 (20%) patients, respectively. The ROC analyses revealed that the cut-off points for predicting death were: BNP > 441 pg/mL, BUN > 1.67 mmol/L, partial pressure in oxygen (PaO2) ≤ 69.7 mmHg, and phase angle < 4.9°. Taken together, these four variables proved to be good predictors for long-term mortality in ADHF (area under the curve [AUC] 0.78, 95% CI 0.72–0.78), thus explaining 60% of all deaths. A multiparametric score based on these variables was determined: each single-unit increase promoted a 2.2-fold augmentation of the risk for death (hazard ratio [HR] 2.2, 95% CI 1.8–2.8, p < .0001). Conclusions. A multiparametric approach based on measurements of BNP, BUN, PaO2, and phase angle is a reliable approach for long-term prediction of mortality risk in patients with ADHF.

Introduction

Heart failure (HF) is defined when structural and/or functional cardiac abnormality promotes reduced cardiac output (CO) and/or elevated intracardiac pressures at rest or during stress [1]. The acute onset of HF results in signs and symptoms mainly related to reduced CO and increased pre-load. Briefly, left ventricular (LV) failure entails the growth of hydrostatic pressure into pulmonary veins, thus promoting interstitial and alveolar oedema. The pulmonary oedema occurring in case of LV failure induces alterations in gas exchange: hypoxia may easily manifest in such conditions, and dyspnoea may become the first symptom of patients with acute HF (AHF).

Arterial blood gas (ABG) analysis is one of the initial steps in clinical evaluation of patients with acute decompensated HF (ADHF). The prognostic implication of gas exchange imbalance in ADHF is still a matter of debate. Little data are about the role of hypoxia and respiratory failure as prognostic determinants in HF, and ADHF in particular.

Minana et al. [2] did not find any correlation between partial pressures of oxygen (PaO2)/carbon dioxide (PaCO2) ratio and prognosis of patients admitted for ADHF. Indeed, the presence of acidosis rather than PaO2 value itself may play a major prognostic role in high risk patients with ADHF [3]. Actually, about half of ADHF patients showed PaO2 ≥ 60 mmHg, and more than one third had normal pH level on ABGs [2–4], thus complicating the evaluation of hypoxia as prognostic factor in ADHF. Nevertheless, alterations in ABG theoretically correlate to central congestion status of ADHF [5].

The congestion plays a key role in HF as it shows diagnostic, prognostic, and therapeutic features within the general management of patients with HF [6]. Bioimpedance vector analysis (BIVA) is an instrument able to evaluate the hydration status of the patient, independently from other acute or chronic HF conditions [7]. Congestion status at...
admission has been demonstrated to correlate with hospital length-of-stay as well as mortality of patients with ADHF [8]. Nonetheless, BIVA alone is not able to comprehensively depict the clinical condition of the patient admitted for ADHF. The combination of clinical, laboratory, and instrumental data deriving from the activity of physicians who are involved in daily hospital practice can provide the right risk and prognosis stratification of patients with ADHF, as well as their therapeutic management [9]. There are no data about the evaluation of correlation between ABG and congestion status in patients with ADHF. The aim of this study was to investigate the influence of ABG and congestion on long-term mortality in patients with ADHF.

**Material and methods**

**Study population**

This was a retrospective study. We included 252 consecutive AHF patients referred to the Cardiology Unit of Altamura Hospital – Bari (Italy) between January 2010 and November 2013. All of the data from patients were gathered from the medical records and included into a dedicated dataset in order to perform the final analyses. The clinical and anthropometric characteristics were computed as well as the comorbidities of the patients. Laboratory data, BIVA measurements, and pharmacological history of the patients were also included.

The patients underwent echocardiographic evaluation in agreement to international guidelines [10]. Briefly, the left ventricular ejection fraction (LVEF) was measured by means of Simpson’s method. According to LVEF and in relation to European Society of Cardiology guidelines, we classify patients into three groups: “reduced LVEF” (<40%), “mid-range LVEF” (between 40% and 49%), and “preserved LVEF” (≥50%) [1].

The exclusion criteria were age <18 years, acute coronary syndrome, recent cardiac surgery intervention, and/or life-threatening malignancy.

The primary endpoint was all-cause mortality. Death was ascertained from medical records when available or from the Italian national database of deaths.

The study complied with the Declaration of Helsinki and was approved by the local Institutional Review Board (protocol n. 0081801/CE—29 October 2015, study number: 4816). Written informed consent was obtained from each patient at inclusion.

**Brain natriuretic peptide**

Brain natriuretic peptide (BNP) levels were measured at admission using a microparticle enzyme immunoassay (Architect, Abbott Park, IL). The intra- and inter-assay variability coefficients ranged from 0.9% to 5.6% and 1.7% to 6.7%, respectively.

**Renal function assessment**

Blood urea nitrogen (BUN) and serum creatinine were measured with a Beckman Coulter AU 680 chemistry analyser. The creatinine clearance, as assessed by means of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, was considered for the assessment of kidney function: male: $141 \times \min (\text{creatinine}/0.9, 1) - 0.411 \times \max (\text{creatinine}/0.9, 1) - 1.209 \times 0.993^{\text{age}} \times 1.159$ (if black); female: $141 \times \min (\text{creatinine}/0.7, 1) - 0.329 \times \max (\text{creatinine}/0.7, 1) - 1.209 \times 0.993^{\text{age}} \times 1.018 \times 1.159$ (if black).

**Arterial blood gas analysis**

ABG at room air was obtained at admission. The ABG parameters considered were: pH, PaCO_{2} (mmHg), PaO_{2} (mmHg), standard bicarbonate (HCO_{3}^{-}, mmol/L), and base excess (BE, normal range: −2 to +2). Acidosis was defined as pH <7.36, and alkalosis as pH >7.44. Hypoxaemia, hypercapnia, and low bicarbonate levels were defined as PaO_{2}<60 mmHg, PaCO_{2}>40 mmHg, and HCO_{3}^{-}<21 mmol/L, respectively. In addition, respiratory failure type I was defined when hypoxaemia was not associated to hypercapnia, while respiratory failure type II when hypoxaemia was associated to hypercapnia [11].

**Bioelectrical phase angle**

The evaluation of bioelectrical phase angle is based on the performance of BIVA. The evaluation of BIVA was performed at admission.

Specifically, the system is endowed with a tetrapolar impedance plethysmography that emits a 330 mA alternating sinusoidal current at a single-frequency of 50 kHz (CardioEFG, Akern RJL Systems, Florence, Italy) [7,12]. Four low-impedance electrodes were used for the performance of the BIVA: two were placed on the right upper arm, the others on the right leg. An alternating-current of 400 mA at 50 kHz was used.

Calibration of device was assessed each day by using a standard resistor (resistance [R] = 380 Ohm, reactance [Xc] = 47 Ohm, 1% error). The two vector components R and Xc were measured in real time and included in a dedicated graph as outlined in previous studies [7,12]. The phase angle (PhA) was obtained by calculating the arc tangent (Xc/R) °180°/π (degrees) [12]. R and Xc normalized by the subject’s height (Ohm/m) were measured simultaneously. PhA was adopted in this study as it has been previously demonstrated as a reliable marker of congestion in patients with acute or chronic HF [13].

**Clinical outcome**

The primary endpoint was all-cause death. After discharge, follow-up was performed by phone call in order to assess survival or death of the patients; when unavailable, National Death Record was consulted.
Statistical analysis

Using the Kolmogorov–Smirnov test, continuous variables were tested for normal distribution. Normally and non-normally distributed continuous variables were expressed as mean (±standard deviation, SD) and median [25th–75th interquartile range (IQR)], respectively. Frequencies of categorical variables were expressed as percentages. Collinearity for each variable that was significant at the univariate analysis was analysed by calculating variance inflation factors (VIF). The VIF values in our model were at acceptable levels – less than 4 – to exclude multicollinearity in our analysis.

Receiver-operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) values, while the optimal cut-off values for mortality were obtained by means of the Youden Index. A Kaplan–Meier survival curve with a log-rank significance test was also performed.

Uni- and multivariate analyses were performed by Cox for proportional hazards and used to analyse the factors associated with all-cause mortality, calculate hazard ratios (HRs), and 95% confidence intervals (CIs). The statistical significance of AUC differences between prognostic variables was also computed by comparing AUC values and standard error (SE) using Wald tests. p Values below .05 were defined as statistically significant. The analyses were made using STATA software version 12 (StataCorp, College Station, TX).

Results

Two hundred fifty-two patients were included in this study. The characteristics of the study population are summarized in Table 1. According to their ABG profile, we could recognize the following conditions: 23 patients (9%) showed acidosis, 34 (14%) normal ABG profile, and 195 (77%) alkalosis. Furthermore, 26 (10%), 82 (33%) and 143 (57%) patients showed low, normal and high BE, respectively. Overall, 98 (39%) had hypoxaemia, 145 (58%) hypercapnia, and 27 (10%) low bicarbonate. In agreement with these results, respiratory failure type I and II could be outlined in 78 (30%) and 53 (20%) patients, respectively.

At a median follow-up of 447 d (IQR: 248–667), 72 patients died after 1–840 d (median 106, IQR: 29–233) after discharge. The median follow-up of the survivors (180 patients) was 562 d (IQR: 384–735). The cumulative mortality rate of the study population was 29%.

The univariate Cox regression analysis showed that BNP, PaO2, and PhA were associated with higher mortality rates, as well as BUN, creatinine, age, and plasma levels of haemoglobin (Table 2). Ischemic dilated cardiomyopathy and de-novo/acute decomposition of chronic HF did not demonstrate a statistically significant association to mortality rate at univariate Cox regression analysis. We included the parameters which resulted significantly related to mortality at univariate regression analysis into a multivariate model. The multivariate Cox regression analysis identified BNP, BUN, PaO2, and Phase Angle as independent predictors for all-cause mortality (Table 2). The creatinine was dropped from the final analysis due to collinearity with BUN.

The ROC analyses revealed that the cut-off points for predicting death were: BNP ≥ 441 pg/mL, BUN > 1.67 mmol/L, PaO2 < 69.7 mmHg, and Pha ≤ 4.9° (Table 3).

Kaplan–Meier analysis indicated a significant increase in mortality rate when the values of each parameter were dichotomized according to previous, calculated cut-offs (Figure 1).

When these four variables were all included in a final multi-marker score, the diagnostic performance of the new, multiparametric approach for predicting mortality in ADHF patients significantly increased (AUC 0.78, 95% CI 0.72–0.78) (Figure 2).

At the end of the follow-up period, no patients with BNP < 441 pg/mL, BUN < 1.67 mmol/L, PaO2 > 69.7 mmHg,
Table 2. Predictive value of clinical, arterial blood gas, and bioimpedance parameters.

| Variables     | Univariate Cox regression analysis | Multivariate Cox regression analysis |
|---------------|------------------------------------|-------------------------------------|
|               | HR (95% CI)                        | p                                  |
| Age, year     | 1.04 (1.01–1.08)                   | 0.001                              |
| LVEF, %       | 0.97 (0.96–1.00)                   | NS                                 |
| BNP, 100 pg/mL| 1.03 (1.02–1.04)                   | <.0001                             |
| Haemoglobin, g/L| 0.81 (0.73–0.91)                   | .0002                              |
| BUN, mmol/L   | 1.02 (1.01–1.03)                   | <.0001                             |
| Creatinine, mmol/L | 1.56 (1.29–1.89)                   | <.0001                             |
| Sodium, mmol/L| 1.02 (0.96–1.08)                   | NS                                 |
| Potassium, mmol/L | 1.07 (0.74–1.54)                   | NS                                 |
| Chloride, mmol/L | 0.99 (0.95–1.03)                   | NS                                 |
| Albumin, mmol/L | 0.80 (0.54–1.19)                   | NS                                 |
| PaO2, mmHg    | 0.97 (0.95–0.99)                   | <.003                              |
| PaCO2, mmHg   | 0.99 (0.97–1.02)                   | NS                                 |
| pH            | 0.99 (0.95–0.99)                   | <.003                              |
| HCO3, mmol/L  | 0.98 (0.9–1.02)                    | NS                                 |
| Standard base excess | 0.98 (0.93–1.02)              | NS                                 |
| Phase angle, degree | 0.59 (0.47–0.75)                | <.0001                             |

HR: hazard ratio; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CI: confidential interval; HCO3: standard bicarbonate; LVEF: left ventricular ejection fraction; PaO2: partial pressure of arterial oxygen.

Table 3. Cut-off points of BNP, BUN, PaO2, and angle phase for death prediction.

| Markers of congestion | Non-survivors (n = 72) | Survivors (n = 180) | AUC (95% CI) | Cut-off | Sensitivity | Specificity | PPV | NPV | p         |
|-----------------------|------------------------|---------------------|--------------|---------|-------------|-------------|-----|-----|-----------|
| BNP, pg/mL            | 1555 (533–2992)        | 514 (202–1089)      | 0.67 (0.57–0.69) | >441    | 82          | 48          | 34  | 87  | <.0001    |
| BUN, mmol/L           | 50 ± 27                | 34 ± 19             | 0.71 (0.66–0.77) | >1.67   | 82          | 56          | 38  | 89  | <.0001    |
| PaO2, mmHg            | 61 ± 11                | 66 ± 13             | 0.63 (0.57–0.63) | <49.7   | 82          | 45          | 38  | 86  | .0006     |
| Phase angle, degree   | 4.4 ± 1.1              | 5.0 ± 1.2           | 0.68 (0.62–0.74) | ≤4.9    | 75          | 44          | 40  | 84  | <.0001    |

AUC: area under the curve; BNP: brain natriuretic peptide; BUN: blood urea nitrogen; CI: confidential interval; PaO2: partial pressure of arterial oxygen; PPV: positive predictive value; NPV: negative predictive value.

Figure 1. Survival curves for all-cause mortality according to brain natriuretic peptide (BNP), blood urea nitrogen (BUN), partial pressure of arterial oxygen (PaO2), and phase angle dichotomized by their optimal cut-off.
and PhA $> 4.9^\circ$ died. Moreover, about 60% of those with abnormal values of all the four parameters died (Figure 3).

Each single-unit increase in this combined score (from 0 to 4) induced a steadily 2.2-fold augmentation of the risk of death (for each unit, HR 2.2, 95% CI 1.8–2.8, \( p < .0001 \)).

**Discussion**

This study mainly demonstrated that: (1) respiratory failure and, specifically, a PaO2 $< 67.9$ mmHg (as assessed by ROC curve), was one of the most important prognostic factors in ADHF; (2) angle phase as assessed by BIVA, BNP, and BUN at admission confirmed to be a determinant of the prognosis of patients with ADHF; (3) PaO2, PhA, BNP, and BUN at admission explained 60% of deaths related to ADHF; and (4) a comprehensive assessment of patients with ADHF should be based on multiparametric approaches with fast and costless markers which can be found in daily clinical practice.

This is the first research which tried to evaluate the impact of ABG on outcome of patients with ADHF in relation to bioimpedance analysis and laboratory findings. Although dyspnoea is one of the most important symptoms in AHF, it is really difficult to assess [14,15]. Moreover, the subjective nature of dyspnoea may not be considered as representative expression of respiratory failure as compared to ABG. Normal profile in ABG could be de facto identified in 37.4% of the overall population of Park et al.’s analysis on the Korean HF (KorHF) registry [3]. Little data are about the role of each ABG determinant at admission on final outcomes in ADHF patients.

Partial pressure of CO2 and BE can act as negative prognostic factors on final outcome of patients with ADHF. Nakano et al. [16] prospectively evaluated ABG analyses in 472 patients with ADHF. They observed that patients with BE $> 2.1$ mmol/L and PaCO2 $> 40$ mmHg showed higher mortality rates as compared to those with values below the indicated limits [16]. On the contrary, univariate regression analysis outlined no relationship between BE/PaCO2 and mortality in our population, thus forcing us not to include such variable in the final, multivariate regression model (Table 2).

Park et al. [3] observed no impact of PaO2 levels on patients’ outcome. Similar results were from Minana et al. [2]: PaO2, PaCO2, and pH were all not related to long-term survival in ADHF. Our study demonstrated that only PaO2 values at admission plays a prognostic role in ADHF patients: values less than 67.9 mmHg predicted mid-term 15% reduction in patients’ survival at 200 d follow-up, which increased up to 20% at long-term follow-up (3 years, Figure 2). ROC curves also revealed the reproducible role of PaO2 as prognostic determinant as compared to well-established biomarkers such as BUN or, better, BNP: there were no differences among these three variables in predicting survival in term of AUC, but rather an improvement in AUC was present only when combining these factors together (Figure 2).

Despite international guidelines [1] do not recommend routine performance of ABG in patients with AHF except for those with peripheral saturation in oxygen (SpO2) $< 90\%$, we do believe that the role of ABG is fundamental for the correct stratification of the risk profile of patients with ADHF.

Our group already demonstrated that a multiparametric approach was able to predict 40% of deaths from HF, independently from acute or chronic type of HF [9]. The present research – focused on ADHF – enforced the predictive value of BNP and BUN. Indeed, the evaluation of congestion by means of BIVA – and angle phase in particular – still continues to demonstrate mid- and long-term impact on evaluating survival in ADHF patients. PhA as assessed by BIVA is a reliable, fast, easy, and reproducible biomarker for evaluation and stratification of HF patients. Alves et al. [17] demonstrated a direct relationship between hydration status and PhA: patients with ADHF and significant congestion

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**Figure 2.** Comparison among ROC curves for the prediction of mortality. Area under the curve (AUC) between combined score and each prognostic marker was statistically significant (combined score vs. brain natriuretic peptide (BNP), \( p = .001 \); combined score vs. blood urea nitrogen (BUN), \( p = .04 \); combined score vs. Phase angle, \( p = .002 \); combined score vs. partial pressure of arterial oxygen (PaO2), \( p = .001 \)).

**Figure 3.** Mortality rate according to the presence of none (\( n = 22 \)), one (\( n = 56 \)), two (\( n = 55 \)), three (\( n = 72 \)), or four (\( n = 47 \)) predictor markers.
showed the highest increase in angle phase during hospitalization, thus impacting on their final outcome. Our group previously demonstrated that PhA was a reliable marker of congestion in patients with acute or chronic HF [13]. PhA was observed to act as a strong predictor of mortality in chronic HF when its value was <4.2° after adjusting for age, haemoglobin levels, and diabetes [18].

Similar results could be outlined in ADHF patients: Alves et al. [19] effectively observed a three-fold increase in mortality rate in ADHF patients when angle phase was <4.8°, after adjusting for age, LVEF, and urea. This datum is similar to that identified by our calculations and corroborates literature [20]: ADHF patients with PhA < 4.9° showed about 25% reduction in survival as compared to those with higher degree (Figure 1).

BUN also showed interesting prognostic values. A two-fold increase in mortality rate could be observed in Veterans, thus determining BUN as independent predictor for worse outcomes [21]. When applied to HF patients, higher BUN values firstly predicted cardiovascular events (mainly cardiovascular death and re-hospitalization) in patients with HF [22–24]. Ren et al. [25] observed the increase of mortality rate in elderly patients with ADHF at short term follow-up of patients with higher BUN: the performance of BUN in predicting death was comparable to BNP. These results were akin to those from the Acute Decompensated HF (ADHF) Syndromes (ATTEND) registry [26]: elevated BUN at admission independently increased the risk of death to 84% in patients with ADHF. Our study enforced data from literature: we demonstrated that BUN independently predicted mortality rate in patients with ADHF, and such result was maintained at long-term follow-up. This constituted the main difference with previous data.

Limitations

The retrospective nature of this article can be considered as a limitation of the study. Indeed, the format of this research allowed us to collect data from a larger dataset of patients suffering with acute HF who were evaluated by bioimpedance analysis for their congestion status. Despite the prognostic role of other biomarkers such as Troponins, we did not evaluate them in our study group. This constitutes the base for future implementation of the study protocol. We did not provide data about therapies at discharge which might impact on final outcomes. Nevertheless, we think that sometimes therapies for HF might not upgraded to the optimal target dose or maximum tolerated dose during the hospital stay, but rather dedicated outpatient evaluations would provide a definite optimization.

Conclusions

PaO₂, BUN, BNP, and PhA as assessed by BIVA predicts long-term mortality in ADHF patients. A multiparametric approach based on these markers could explain the 60% of long-term death of patients admitted for ADHF. For the first time, respiratory failure became a reliable predictor of long-term worse prognosis in ADHF, thus promoting the role of ABG analysis for the comprehensive evaluation and risk stratification of these patients.

Disclosure statement

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