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Assessment of phosphatemia at admission to the intensive care unit to predict mechanical ventilation among patients with acute exacerbation of chronic obstructive pulmonary disease: a retrospective cohort study

Sylvain Diop[1,2]^, Stéphane Legriel[1,3], Alexis Ferré[1]

[1]Intensive Care Unit, Versailles Hospital, Le Chesnay, France; [2]Department of Anesthesiology and Intensive Care, Marie Lannelongue Hospital, Le Plessis Robinson, France; [3]University Paris-Saclay, UVSQ, INSERM, CESP, Team "PsyDev", Villejuif, France

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Correspondence to: Sylvain Diop, MD. Department of Anesthesiology and Intensive Care, Marie Lannelongue Hospital, 133 Avenue de la Résistance, 92350 Le Plessis Robinson, France; Intensive Care Unit, Versailles Hospital, 177 Avenue de Versailles, 78150 Le Chenay, France. Email: menes.diop@gmail.com.

Background: Hypophosphatemia has been reported to impair diaphragmatic function in patients with chronic obstructive pulmonary disease (COPD). However, little is known about the role of dysphosphatemia at admission [plasmatic phosphate concentration at intensive care unit (ICU) admission (T0-Ph)] to the ICU and respiratory outcomes among patients with severe acute COPD exacerbation. We aimed to assess the value of T0-Ph as a predictive factor of invasive mechanical ventilation (MV) during ICU stay.

Methods: We retrospectively included consecutive patients admitted to the ICU for a severe acute exacerbation of COPD between May 2015 and December 2018. Logistic multivariate regression analysis was performed to identify association between T0-Ph and the need for invasive MV during the ICU stay.

Results: We included 198 patients of whom 132 (67%) were male. The median age was 70 [interquartile range (IQR), 61–77] years. Nine (4.5%) patients died in the ICU. Median T0-Ph was significantly higher among patients requiring invasive MV as compared to non-intubated patients [1.23 (IQR, 1.07–1.41) and 1.09 (IQR, 0.91–1.27) mmol/L; P=0.005]. By multivariate analysis, pneumonia [odds ratio (OR) =6.42; 95% confidence interval (CI): 2.78–15.96; P<0.0001) and a history of intubation (OR =3.33; 95% CI: 0.97–11.19; P=0.05) were independently associated with the need for invasive MV, whereas T0-Ph was not (OR =1.75; 95% CI: 0.72–4.44; P=0.22).

Conclusions: T0-Ph was significantly higher in patients requiring invasive MV. However, T0-Ph was not associated with the need for invasive MV in multivariate analysis.

Keywords: Chronic obstructive pulmonary disease (COPD); exacerbation; phosphate (Ph); respiratory failure; mechanical ventilation (MV); intensive care unit (ICU)

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^ ORCID: 0000-0002-6846-8254.

Introduction

Severe acute exacerbation of chronic obstructive pulmonary disease (COPD) is a common cause of admission to the intensive care unit (ICU). It is associated with significant morbidity, mortality, and economic burden (1,2). First line management in ICU consists of the treatment of the triggering factor, if identified, and implementation of non-invasive ventilation (NIV) (2-5). Acute respiratory failure related to COPD exacerbation is a consequence of lung dynamic hyperinflation and increased work of breathing (6). It leads to a higher oxygen and energetic consumption of respiratory muscles that could override the aerobic production of adenosine tri phosphate (ATP) into mitochondria. As a major compound of ATP, phosphate (Ph) could be a simple marker of the intracellular energetic pool (7,8). At the bedside, only plasmatic Ph is easily available. Some studies showed that a low plasmatic Ph concentration is associated with a decreased diaphragmatic contractility (9) and invasive mechanical ventilation (MV) weaning failure (10-12). Dysphosphatemia is a frequent finding in ICU particularly among patient suffering from COPD with a prevalence of hypophosphatemia up to 21.5% (7). Until now, clinical implication of plasmatic Ph concentration at ICU admission (T0-Ph) on respiratory outcomes during acute respiratory failure related to COPD remains unclear.

Highlight box

Key findings

- Hypophosphatemia at admission to the intensive care unit (ICU) was not associated with the need for invasive mechanical ventilation (MV).

What is known and what is new?

- Hypophosphatemia has been associated with MV weaning failure among mechanically ventilated chronic obstructive pulmonary disease (COPD) patients. However, data regarding the association between plasmatic phosphate level at ICU admission (T0-Ph) and the need for invasive MV during ICU stay are scarce.
- T0-Ph was not associated with the need for invasive MV. At the contrary, T0-Ph was higher in patients requiring invasive MV, but not associated with the need for invasive MV in multivariate analysis.

What is the implication, and what should change now?

- Larger prospective studies are needed to better investigate the association between T0-Ph and respiratory outcomes. In the meantime, it is costless to consider that a high T0-Ph value, could be a warning signal, acute respiratory failure related to COPD exacerbation.

We hypothesize that hypophosphatemia (i.e., below 0.80 mmol/L) at admission to ICU is associated with worse respiratory outcomes. So, the aim of the present study is to investigate the association between T0-Ph and the need for invasive MV among patients with severe acute exacerbation of COPD. We present this article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1650/rc).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This single-center, observational, retrospective study was approved by the ethics committee of the French Intensive Care Society (No. #20-12) and registered at the French National Institute for Health Data (#MR 2516271119). According to French law, all patients included were informed to the use of their medical data for the study purpose and their right to refusal to participate at any time. Informed consent was sought from the patients upon recovery of competency, in compliance with French law. The 28-bed ICU is in a university-affiliated tertiary hospital in the Paris area with 800 medical and surgical beds.

Patients

We screened all consecutive patients admitted to our ICU between May 2015 and December 2018 with COPD as a confirmed or strongly suspected comorbidity [patient over 40 years old reporting chronic respiratory symptoms due to chronic bronchitis according to Global Initiative for Obstructive Lung Disease (GOLD) criteria (1) and a history of smoking for more than 5 years]. Only patients over 40 years of age admitted for a severe acute exacerbation of COPD were included. COPD was defined according to GOLD criteria (1).

Exclusion criteria were the use of invasive MV before admission to the ICU, patients without T0-Ph plasma measurement, patients deceased in ICU with a decision of do not intubate or do not resuscitate, patients with a specific contraindication of NIV (surgery, deformity or facial trauma, or digestive intolerance with uncontrollable vomiting making NIV impossible), known asthma according to the Global Initiative for Asthma definition (13).

Definition

Severe acute exacerbation of COPD

Severe acute exacerbation of COPD was defined by

the presence of acute respiratory failure (clinical signs of excessive muscle activity, polypnea ≥30 breaths/min, or the use of accessory respiratory muscles) and/or hypercapnic acidosis [pH ≤7.35 and carbon dioxide tension ($PaCO_2$) >45 mmHg], and the need for ICU admission.

Pneumonia

Pneumonia was defined as the presence of at least two of the following criteria: auscultatory crackles, purulent sputum or tracheal suction (for intubated patients), fever >38 ℃, and biological inflammatory syndrome; associated with a new radiological infiltrate (chest X-ray or computed tomography scan).

Bronchitis

Bronchitis was defined as the presence of dyspnoea or cough with purulent expectorations or tracheal suction (for intubated patients) without a new radiological infiltrate.

Phosphatemia

Plasmatic Ph reference value according to our laboratory was 0.80 to 1.15 mmol/L (2.48–3.56 mg/dL).

Patient management

Ventilatory support

According to international guidelines for patients with severe acute exacerbation of COPD, NIV was used as first-line therapy for signs of respiratory failure with respiratory acidosis, e.g., pH ≤7.35 and hypercapnia with $PaCO_2$ ≥45 mmHg (14). Intermittent NIV was pursued for 24 hours period until clinical improvement with progressive weaning. The formal indications for invasive MV were standardized: (I) NIV failure (neurological worsening with persistent hypercapnic acidosis; respiratory and hypercapnic acidosis worsening; refractory hypoxemia under NIV); (II) cardiac arrhythmias leading to circulatory failure; (III) shock requiring a vasopressor; (IV) cardiopulmonary arrest.

Screening for respiratory tract infection

A search for bacteria with standard methods and for viruses with sensitive methods (i.e., polymerase chain reaction) was performed in all patients admitted for a severe acute exacerbation of COPD in case of suspected respiratory infection according to the standards of care in our ICU at admission.

Plasmatic Ph sample and management

Blood Ph was sampled at ICU admission in our routine practice. In case of abnormal results (i.e., below 0.80 mmol/L or above 1.15 mmol/L) a second sample was performed between 12 and 24 hours later. For patients with T0-Ph below 0.80 mmol/L, an intravenous infusion of Ph was initiated (Phocytan™ 0.66 mmol/mL, Aguettant, France).

Data collection

All collected data were obtained retrospectively from medical records into a standardized electronic file, secured and anonymized (Excel, Microsoft©, Redmond, WA, USA). Data collection included age; gender; chronic comorbidities; COPD assessment, triggering factor for the exacerbation; performance status; Simplified Acute Physiology Score II (SAPS II); clinical parameters, neurologic impairment and Glasgow Coma Scale (GCS) at ICU admission; laboratory tests (including electrolytes blood sample, phosphatemia at ICU admission and during the first 24 hours after admission, arterial blood gas); type and duration of ventilatory assistance (oxygen administration, NIV, invasive MV); time from ICU admission to intubation, length of stay in the ICU and in-hospital, and mortality in the ICU. Missing data are reported in the results tables.

Statistical analysis

No specific sample size calculation was made. We include patients from May 2015 as it corresponds to the time of implementation of informatized medical records and prescriptions in the ICU. Quantitative parameters were described as median [interquartile range (IQR)] and qualitative parameters as number (percentage). We compared categorical variables using Fisher's exact test, continuous variables using the Wilcoxon rank-sum test, and ordered categorical variables using Chi-squared and Kruskal-Wallis tests. We performed logistic regression to identify factors associated with the need for MV. Continuous variables were checked for log-linearity. Non-log-linear variables were transformed into dummy variables according to their inflexion point or median value. The following continuous variables were transformed into binary variables: pH with a cut-off value of 7.33, phosphatemia with a cut-off value of 1.11 mmol/L, and GCS with a cut-off value of 15. Non-collinear variables that yielded P

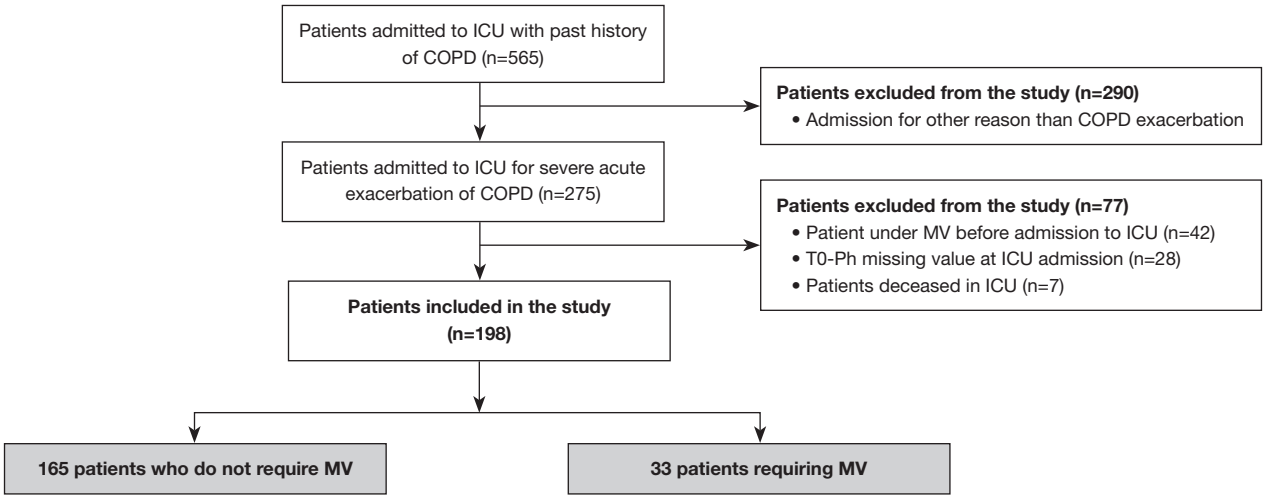

Figure 1 Patients flow chart. ICU, intensive care unit; COPD, chronic obstructive pulmonary disease; T0-Ph, plasmatic phosphate concentration at ICU admission; MV, mechanical ventilation.

values smaller than 0.001 by univariate analysis or that were clinically relevant were considered for inclusion into a multivariable model. Stepwise model selection guided by the Akaike Information Criterion was performed. The Hosmer-Lemeshow goodness-of-fit test and area under the receiver operating characteristics curve estimated by the C-statistic were computed on the final models. Associations of factors with the need for MV during the ICU stay are reported as odds ratios (ORs) with their 95% confidence intervals (CIs). All tests were two sided, and P values <0.05 were considered significant. The analyses were performed using the R statistical programme, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org).

Results

Patient's characteristics

Figure 1 is the patient flowchart and *Table 1* reports patient characteristics at ICU admission. One hundred and ninety-eight patients were included, of whom 132 (66.7%) were men. The median age was 70 [IQR, 61–77] years; the median SAPS II was 38 [IQR, 31–45]. Nine (4.5%) patients died in the ICU. Among the 167 (84%) patients with available lung spirometry data, 80 (40.4%) had a GOLD classification COPD stage 4, 40 (20.2%) stage 3, 35 (17.7%) stage 2, and 12 (6.1%) stage 1. The main final etiology of exacerbation of COPD was pneumonia in 68 (34.3%), bronchitis in 26 (13.1%), and acute cardiogenic pulmonary oedema in 32 (16.2%) patients. In 29 (14.6%) patients, no trigger was identified. Other causes for exacerbation are described in *Table 1*.

Laboratory findings at admission, patient management and outcomes

Laboratory findings at ICU admission, patient management and outcomes are reported in *Table 2*. pH was significantly lower and $PaCO_2$ was higher in patient requiring invasive MV (7.30 *vs.* 7.34, P=0.0006 and 64 *vs.* 57 mmHg, respectively, P=0.041) whereas plasmatic bicarbonate concentration was not. Among the 198 patients included, 134 (67.7%) were under NIV and 64 (32.3%) under oxygen therapy at ICU admission. During ICU stay, 33 (16.7%) patients required invasive MV. Median duration of NIV and invasive MV were 3 [IQR, 1–4] and 7 [IQR, 3–13] days respectively. The median time between admission and initiation of invasive MV was 5 [IQR, 2–12] hours. The median length of stay in the ICU for the non-intubated and intubated patients was 5 [IQR, 3–7] and 13 [IQR, 7–19] days, respectively.

Factors associated with the need for invasive MV

Univariate analysis is reported in *Table 3*. T0-Ph was significantly higher among patient requiring invasive MV compared to those who did not [1.23 (IQR, 1.07–1.41) and 1.09 (IQR, 0.91–1.27) mmol/L; P=0.005]. A T0-Ph >1.11 mmol/L

Table 1 Patient characteristics at ICU admission

Variables	All patients (n=198, 100%)	Patients not requiring invasive MV (n=165, 83.3%)	Patients requiring invasive MV (n=33, 16.7%)	P value	N missing[†]
Demographic characteristics					
Age (years)	70 [61, 77]	69 [60, 77]	72 [67, 78]	0.11	–
Male sex	132 (66.7)	110 (66.7)	22 (66.7)	0.46	–
Body mass index (kg/m^2)	25.6 [21.7, 31.0]	25.4 [21.4, 31.2]	26.2 [22.2, 29.4]	0.71	–
Active smoking	195 (98.5)	162 (98.2)	33 (100.0)	0.98	–
COPD history					31
Stage 1 (GOLD)	12 (6.1)	12 (7.3)	0 (0.0)	0.22	–
Stage 2 (GOLD)	35 (17.7)	31 (18.8)	4 (12.1)	0.46	–
Stage 3 (GOLD)	40 (20.2)	33 (20.0)	7 (21.2)	0.93	–
Stage 4 (GOLD)	80 (40.4)	67 (40.6)	13 (39.4)	0.30	–
History of intubation for COPD exacerbation	18 (9.1)	11 (6.7)	7 (21.2)	0.036	2
Long-term oxygen therapy	77 (38.9)	69 (41.8)	8 (24.2)	0.12	–
Long-term home care NIV	42 (21.2)	39 (23.6)	3 (9.1)	0.092	–
Chronic use of oral steroids	24 (12.1)	20 (12.1)	4 (12.1)	0.96	–
Comorbidities					
Coronary artery disease	39 (19.7)	32 (19.4)	7 (21.2)	0.41	–
Treated arterial hypertension	110 (55.6)	90 (54.5)	20 (60.6)	0.91	–
Diabetes mellitus	38 (19.2)	29 (17.6)	9 (27.3)	0.17	–
Chronic kidney failure	17 (8.6)	13 (7.9)	4 (12.1)	0.77	11
Characteristics at ICU admission					
SAPS II	38 [31, 45]	36 [29, 42]	54 [44, 62]	<0.0001	–
Glasgow Coma Scale	15 [14, 15]	15 [14, 15]	15 [12, 15]	0.0008	–
Triggering factor of exacerbation					
Pneumonia	68 (34.3)	45 (27.3)	23 (69.7)	<0.0001	–
Bronchitis	26 (13.1)	24 (14.5)	2 (6.1)	0.19	–
Cardiogenic pulmonary edema	32 (16.2)	29 (17.6)	3 (9.1)	0.24	–
Pulmonary embolism	6 (3.0)	6 (3.6)	0 (0.0)	0.75	–
Therapeutics inobservance	12 (6.1)	11 (6.7)	1 (3.0)	0.29	–
Pleural disease	5 (2.5)	4 (2.4)	1 (3.0)	0.70	–
New/change of psychotropic treatment	13 (6.6)	11 (6.7)	2 (6.1)	0.39	–
Others causes	7 (3.5)	6 (3.6)	1 (3.0)	>0.99	–
Non-identified trigger	29 (14.6)	29 (17.6)	0 (0.0)	0.005	–

Data are presented as n (%) or median [interquartile range]. [†], number of missing observations, unless Ø (empty set). ICU, intensive care unit; MV, mechanical ventilation; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; NIV, non-invasive ventilation; SAPS II, Simplified Acute Physiology Score II.

Table 2 Laboratory tests, patient management and outcomes

Variables	All patients (n=198, 100%)	Patients not requiring invasive MV (n=165, 83.3%)	Patients requiring invasive MV (n=33, 16.7%)	P value
Laboratory tests at ICU admission				
T0-Ph (mmol/L)	1.11 [0.92, 1.30]	1.09 [0.91, 1.27]	1.23 [1.07, 1.41]	0.005
pH	7.33 [7.27, 7.37]	7.34 [7.28, 7.37]	7.30 [7.19, 7.34]	0.0006
PaO_2 (mmHg)	77.5 [64, 94]	76 [63, 91]	87 [75, 99]	0.023
$PaCO_2$ (mmHg)	58 [47, 74]	57 [47, 72]	64 [52, 75]	0.041
HCO_3^- (mmol/L)	31.0 [26.3, 35.9]	31.0 [26.0, 37.0]	30.0 [27.0, 34.0]	0.57
SaO_2 (%)	94 [91, 97]	94 [91, 96]	95 [92, 98]	0.80
Lactate (mmol/L)	1.3 [0.9, 1.7]	1.2 [0.9, 1.7]	1.3 [1.0, 1.8]	0.96
Serum creatinine (µmol/L)	70 [53, 96]	69 [53, 94]	72 [61, 105]	0.033
Serum albumin (g/L)	33 [28, 36]	34 [29, 37]	30 [26, 34]	0.025
Plasmatic phosphate variation at 24 hours				
24 hours-phosphate (mmol/L)	0.99 [0.84, 1.2]	1.04 [0.85, 1.21]	0.91 [0.7, 1.1]	0.01
Delta phosphate between ICU admission and 24 hours (mmol/L)	–0.11 [–0.38, 0.08]	–0.04 [–0.23, 0.15]	–0.42 [–0.53, –0.18]	0.0001
ICU management				
NIV	179 (90.4)	149 (90.3)	30 (90.9)	0.58
Diuretics during ICU stay	45 (22.7)	41 (24.8)	4 (12.1)	0.27
Vasoactive drugs	8 (4.0)	1 (0.6)	7 (21.2)	NA
Ventilator acquired pneumonia	7 (3.5)	–	7 (21.2)	–
NIV after ICU discharge	57 (28.8)	54 (32.7)	3 (9.1)	0.010
Patients receiving phosphate supplementation during the first 24 hours	38 (19.2)	30 (18.2)	8 (24.2)	0.47
Volume of phosphate supplementation (Phocytan™ 0.66 mmol/mL) (mL) during the first 24 hours	30 [20, 40]	30 [20, 40]	25 [17.5, 40]	0.39
Outcomes				
Duration of NIV (days)†	3 [1, 4]	3 [2, 5]	2 [1, 3]	0.13
Duration between admission and initiation of invasive MV (hours)	5 [2, 12]	–	5 [2, 12]	–
Duration of invasive MV (days)	7 [3, 13]	–	7 [3, 13]	–
ICU length of stay (days)	5 [3, 8]	5 [3, 7]	13 [7, 19]	<0.0001
ICU mortality	9 (4.5)	0 (0.0)	9 (27.3)	<0.0001

Data are presented as n (%) or median [interquartile range]. †, for the group of patients requiring invasive MV duration of NIV corresponds to the total duration of NIV, meaning before initiation and after weaning of invasive MV. MV, mechanical ventilation; ICU, intensive care unit; T0-Ph, plasmatic phosphate concentration at ICU admission; NIV, non-invasive ventilation; NA, non-available data.

was associated with the need for invasive MV (OR =2.25; 95% CI: 1.14–4.41; P=0.019) whereas T0-Ph <0.80 mmol/L was not (OR =2.38; 95% CI: 0.54–21.9; P=0.38). Other factors were pneumonia (OR =5.66; 95% CI: 2.79–11.5; P=0.0001) and pH <7.33 at ICU admission (OR =2.77; 95% CI: 1.41–5.44; P=0.003).

Table 4 reports the multivariate analysis of factor associated with the need for invasive MV. Pneumonia (OR

Table 3 Univariate analysis of risk factors associated with the need for invasive mechanical ventilation

Variables	Patients not requiring invasive MV (n=165)	Patients requiring invasive MV (n=33)	Univariate analysis		
			OR	95% CI	P value
Age (years)	69 [60, 77]	72 [67, 78]	1.03	0.99–1.06	0.11
Male sex	55 (33.3)	11 (33.3)	0.78	0.41–1.51	0.46
SAPS II	36 [29, 42]	54 [44, 62]	1.08	1.05–1.11	0.0001
Pneumonia	44 (26.7)	24 (72.7)	5.66	2.79–11.5	0.0001
GCS at admission	15 [14, 15]	15 [12, 15]	0.89	0.83–0.95	0.0008
History of intubation for COPD exacerbation	11 (6.7)	7 (21.2)	2.59	1.07–6.30	0.036
Arterial blood gas parameters					
pH	7.34 [7.28, 7.37]	7.30 [7.19, 7.34]	0.00	0.00–0.04	0.0006
PaO_2 (mmHg)	76 [63, 91]	87 [75, 99]	1.01	1.00–1.01	0.023
$PaCO_2$ (mmHg)	57 [47, 72]	64 [52, 75]	1.02	1.00–1.03	0.041
HCO_3^- (mmol/L)	31 [26, 37]	30 [27, 34]	0.99	0.94–1.04	0.57
Serum albumin (g/L)	34 [29, 37]	30 [26, 34]	0.94	0.89–0.99	0.025
T0-phosphate (mmol/L)	1.09 [0.91, 1.27]	1.23 [1.07, 1.41]	2.97	1.39–6.36	0.005
Serum creatinine (µmol/L)	69 [53, 94]	72 [61, 105]	1.01	1.00–1.01	0.033
pH at ICU admission <7.33	70 (42.4)	22 (66.7)	2.77	1.41–5.44	0.003
Age >70 years	80 (48.5)	20 (60.6)	1.77	0.92–3.40	0.087
Serum albumin >32 g/L	70 (42.4)	11 (33.3)	0.51	0.24–1.05	0.069
T0-phosphate >1.11 (mmol/L)	76 (46.1)	21 (63.6)	2.25	1.14–4.41	0.019
T0-phosphate <0.80 (mmol/L)	22 (13.3)	2 (6.1)	2.38	0.54–21.9	0.38
GCS at ICU admission <15	47 (28.5)	16 (48.5)	2.48	1.30–4.75	0.006

Data are presented as number (%) or median [interquartile range]. MV, mechanical ventilation; OR, odds ratio; CI, confidence interval; SAPS II, Simplified Acute Physiologic Score II; GCS, Glasgow Coma Scale; COPD, chronic obstructive pulmonary disease; T0-phosphate, plasmatic phosphate concentration at ICU admission; ICU, intensive care unit.

Table 4 Multivariate analysis of risk factors associated with the need for invasive mechanical ventilation

Variables	Multivariate analysis		
	OR	95% CI	P value
Pneumonia	6.42	2.78–15.96	<0.0001
T0-phosphate >1.11 mmol/L	1.75	0.72–4.44	0.22
pH <7.33	2.23	0.93–5.57	0.07
History of intubation for previous COPD exacerbation	3.33	0.97–11.19	0.05

Hosmer and Lemeshow test, P value: 0.91. AUROC: 0.80. OR, odds ratio; CI, confidence interval; T0-phosphate, plasmatic phosphate concentration at ICU admission; COPD, chronic obstructive pulmonary disease; AUROC, area under the receiver operating characteristic curve; ICU, intensive care unit.

=6.42; 95% CI: 2.78–15.96; P<0.0001) and previous history of intubation (OR =3.33; 95% CI: 0.97–11.19; P=0.05) were independently associated with the need for invasive MV, whereas T0-Ph was not (OR =1.75; 95% CI: 0.72–4.44; P=0.22).

Variation of phosphatemia after ICU admission according to the ventilatory support

Plasmatic Ph sample at 24 hours was available for 87.9% (29/33) patients that required invasive MV and for 74.5% (123/165) patients who did not. At 24 hours, plasmatic Ph concentration was significantly lower among patients requiring invasive MV as compared to others [0.91 (IQR, 0.7–1.10) and 1.04 (IQR, 0.85–1.21) mmol/L, respectively; P=0.01]. The variation of Ph at 24 hours was significantly lower among non-intubated patients as compared to intubated patients [–0.04 (IQR, –0.225, 0.15) and –0.42 (IQR, –0.53, 0.18) mmol/L, respectively; P=0.0001]. Ph supplementation was administered to eight patients that required MV and in 30 (18.2%) patients in others. The median volume of Ph supplementation (Phocytan™ 0.66 mmol/mL) was 25 [IQR, 17.5–40] and 30 [IQR, 20–40] mL in patients requiring MV and those not respectively.

Discussion

We aimed to investigate the association between T0-Ph and ventilatory outcomes among patients admitted to the ICU for severe acute exacerbation of COPD. Hypophosphatemia (i.e., T0-Ph <0.80 mmol/L) was not associated with the need for invasive MV. At the contrary, our results showed that T0-Ph was significantly higher in patient requiring invasive MV during ICU stay. However, by multivariate analysis, we found no significant association between T0-Ph and the need for invasive MV. Patients' characteristics included in our cohort, predominantly men, median age of 70 years old, with pneumonia as main trigger of COPD exacerbation were similar to those of previous large studies on this population (15-18). The rate of patient requiring invasive MV (17%, 33/198) and the median duration of invasive MV (5 days) were similar to other studies (18,19). As compared to previous studies of populations with similar baseline characteristics, we report a lower mortality rate in our study (4.5%) (15,17). This difference could be related to differences in selection criteria for ICU admission and inclusion in the study as only non-intubated patients at ICU admission were included.

Hypophosphatemia is a frequent finding and associated with worse outcomes in ICU (20,21). In a previous study, Aubier *et al.* measured the transdiaphragmatic pressure at different plasmatic Ph concentration in eight patients receiving invasive MV for acute respiratory failure related to COPD within the 12 hours after admission to ICU. They found a decrease transdiaphragmatic pressure correlated with the level of hypophosphatemia. After Ph supplementation a recovery of the diaphragmatic contractility was observed (9). Similarly, Gravelyn *et al.* measured the muscular strength in 23 patients recruited from medical and surgical center. Plasmatic Ph level was assessed daily during a 30 days study-period and ranked into normal or hypophosphatemia group (Ph level below 0.80 mmol/L). They found that hypophosphatemia was associated with increased muscular weakness (22). Others clinical studies reported that hypophosphatemia was associated with weaning failure of invasive MV (10-12). In a single-center, prospective study including 100 patients admitted to the ICU, Talakoub *et al.* found a significant association between plasmatic Ph level at ICU admission and the duration of invasive MV with a Ph level of 1.10 (±0.13) and 0.93 (±0.10) mmol/L in patients receiving invasive MV for less than 5 days and for more than 5 days respectively (P<0.001) (12). Another prospective study including 66 patients showed that the plasmatic Ph concentration was significantly lower among patient who failed their invasive MV weaning trials [relative risk (RR) =1.18; 95% CI: 1.06–1.32; P=0.01] (10). A retrospective study including 67 patients also found that a low plasmatic Ph concentration was associated with an increased risk of invasive MV weaning failure (11). Whereas, hypophosphatemia seems to be frequently associated with worse respiratory outcomes in the literature, our results showed that T0-Ph was higher in patient requiring invasive MV during their stay in. However, it could be explained by several adaptive physiological mechanisms. The increased work of breathing observed in case of severe acute exacerbation of COPD leads to a higher metabolic demand in respiratory muscles (23). Among the most severe patients, ATP synthesis becomes insufficient reflected by a rapid decrease in intracellular ATP and phosphocreatine level. Inorganic Ph and adenosine di-phosphate resulting from the degradation of ATP increase proportionally (24). Patients also develop intracellular acidosis resulting from the increase of both $PaCO_2$ and lactate production (25,26). This excess of intracellular acid load has to be scavenged and inorganic Ph (acid-basis couple: $HPO_4^{2-}/H_2PO_4^-$) has been identified

to be an important intracellular buffer system (27,28). Because the respiratory system is compromised during severe acute exacerbation it cannot maintain pH between physiological values. The pH regulation system depends on renal response through reabsorption of sodium cation and excretion of chloride anion (to increase the strong ion difference) and organic acids. A previous physiological study showed that metabolic and respiratory acidosis both increase plasmatic Ph concentration and phosphaturia presumably to enhance titratable acids excretion (28). A transient high plasmatic Ph concentration could result from a higher intracellular inorganic Ph production and acid load. It could therefore reflect the severity of the intracellular energetic crisis. Our results are consistent with this physiological hypothesis: Plasmatic Ph concentration was higher in patient who required invasive MV and decreased abruptly after its initiation (–0.42 mmol/L at 24 hours). As in our study, Laaban *et al.* also found that plasmatic Ph concentration decreased significantly after initiation of invasive MV in patients with COPD (29). It is presumably linked to the correction of the respiratory acidosis and the resting of the respiratory muscle that led to a shift of Ph into the intracellular space, to restore cellular ATP and phosphocreatine supplies through the stimulation of the glycolysis and the production of sugar Ph (30). Lactate level at admission was similar in both group of patients suggesting that the anaerobic metabolism was not predominant in the patients needing invasive MV. However, we only report lactate at admission and not its variation over the time particularly the first 24 hours thus limiting the meaning of this single value as a marker of the anaerobic metabolism.

Our preliminary findings were not confirmed in the multivariate analysis. One plausible explanation is that plasmatic Ph is a dependent variable influenced by numerous factors encountered in ICU such as drugs administration, ventilation modalities, renal excretion and acid base status. A well-designed prospective study is needed to confirm or infirm our hypothesis.

In multivariate analysis, pneumonia and previous history of intubation was associated with the need for invasive MV. These findings are consistent with previous studies, in which pneumonia is one of the main risk factors of intubation in COPD patients (31,32).

Several limitations of our study must be acknowledged. First, this is a single-center retrospective study; thus, the interpretation and generalization of the results are limited but the characteristics of our patients are similar to those of previous large studies. Second, the limited sample size (198 patients) does not allow highlighting all potential risk factors. For 31 (16%) patients lung spirometry data were not available, and COPD was presumed according to the definition used in the method section. Third, important data such as phosphaturia was not monitored, it would have been helpful to determine in which proportion acid load was eliminated through the Ph buffer between the two groups of patients. Most of the patients received additional therapy such as corticosteroids or beta-2 bronchodilators which stimulates renal Ph excretion and could disturb physiological Ph homeostasis. Data regarding the time between admission from emergency ward and ICU was not available, some therapeutics initiated before ICU admission could have influenced plasmatic Ph value. Fourth, the plasmatic Ph concentration is easily available at the bedside, but clinical meaning of T0-Ph remained undetermined. It could reflect the severity of the exacerbation, the consequences of respiratory acidosis, a compensatory mechanism triggered by the intracellular acidosis, or all at the same time.

Further clinical studies with close monitoring of plasmatic Ph concentration and phosphaturia would be helpful to determine the relevance of this biological marker as a predictive factor of invasive MV. In the meantime, it is costless to consider that a high T0-Ph value, could be a warning signal among others, in COPD patients admitted to ICU for acute respiratory failure.

Conclusions

Among patient admitted to the ICU for severe acute exacerbation of COPD, T0-Ph was significantly higher in patients requiring invasive MV as compared to the group of non-intubated patients. However, T0-Ph was not associated with the need for invasive MV in multivariate analysis. Larger multicentric and prospective studies are needed to better investigate the association between T0-Ph and respiratory outcomes.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1650/coif). A.F. reports honoraria by Fisher & Paykel for a lecture during French Society of emergency medicine (SFMU) Congress 2022, outside the submitted work. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This single-center, observational, retrospective study was approved by the ethics committee of the French Intensive Care Society (No. #20-12) and registered at the French National Institute for Health Data (#MR 2516271119). Informed consent was sought from the patients upon recovery of competency, in compliance with French law.

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