

Effect of hypophosphatemia on weaning from mechanical ventilation of chronic obstructive pulmonary disease patients during acute exacerbations

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Abstract

Background: Mechanical ventilation (MV) is a machine used to help people who are very sick and having trouble breathing. It can support or take over their breathing for them. **Aim of the study:** evaluate the predictive value of serum phosphorus level on weaning of mechanically ventilated COPD patients with acute exacerbation. **Patients and Methods:** This study was a prospective investigational study carried out on **70** mechanically ventilated (MV) patients with acute exacerbation of COPD. According to phosphorus level, patients were classified into two groups, Group I :Normal phosphorus level group (Ph 2.5 – 4.5 mg/dL). Group II :low phosphorus level (Hypophosphatemia) group (Ph <2.5 mg/dL). **Results:** Patients with normal phosphate level have statistically significantly higher age and BMI than those with hypophosphatemia. There is no statistically significant difference between other vital data, hematological data, ABG data, biochemical data and serum electrolytes level of patients with and without hypophosphatemia. Patients with hypophosphatemia have statistically significant higher rate of difficult weaning and longer duration of mechanical ventilation than those with normal phosphate. There is statistically significant lower serum phosphate level in patients with difficult weaning than easy weaning group. Serum level of phosphate has statistically significant negative correlation with The age, BMI, duration of MV, HR,RR, PCO2 and has statistically significant positive correlation with PH, at cut off level of <3.05, serum phosphate had sensitivity of 82.1% and specificity of 81.8% for predicting difficult weaning from MV. **Conclusion:** Based on past findings, having low levels of phosphorus in the blood (hypophosphatemia) is linked to a worse outcome for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). Those with hypophosphatemia may need to be assessed early to determine their level of risk for difficult weaning from mechanical ventilation. **Keywords:** Weaning, Ventilation, phosphorus, chronic obstructive lung disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent airflow limitation that is usually progressive and is associated with a chronic enhanced inflammatory response in the airways and lungs to noxious particles and gases.

Mechanical ventilation (MV) is a machine used to help patients who are very sick, like those with severe breathing problems, by using a machine to take over or assist their breathing. This is often done in cases of acute worsening of chronic obstructive pulmonary disease (AECOPD).

MV helps with breathing by ventilating the lungs. It cannot cure any underlying disease, but it can cause problems like lung injury, difficulty breathing, collapsed lung, and pneumonia.

Although there are no specific rules that apply to all patients, it is important to not unnecessarily delay withdrawing patients from mechanical ventilation, which is also known as weaning.

Previous research has shown that hypophosphatemia (Ph <2.5 mg/dL) was associated with poor prognosis in terms of longer durations of mechanical ventilations and difficult weaning in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Patient and Methods

This study was a prospective investigational study carried out on **70** mechanically ventilated (MV) patients with acute exacerbation of COPD. These patients were admitted to the critical care units at Benha University Hospital and Alexandria University Hospital at a period between (January 2022 - may 2023).

After getting permission from the medical ethics committees of Benha Faculty of Medicine and Alexandria Faculty of Medicine, we asked the patient's close family member for their agreement to use their information in this study.

According to phosphorus level, patients were mentioned as two groups:-

- Group I :Normal phosphorus level group (Ph 2.5 – 4.5 mg/dL)
- Group II :low phosphorus level (Hypophosphatemia) group (Ph <2.5 mg/dL).

Inclusion criteria:

- Adult patients (≥ 18 years old)
- patients with acute exacerbation of COPD on invasive MV (endotracheal tube or tracheostomy tube)
- Both genders are eligible for the study.

Exclusion criteria:

- Pregnant females.
- Patients under phosphorus compounds treatment or parenteral nutrition containing phosphorus.
- Patients who are on calcium supplements.
- chronic renal failure, acute cerebrovascular disease, malignancy, bronchial asthma, and severe sepsis or any other severe inflammatory illness.

Methods

All enrolled patients (n=70) were subjected directly after admission to the followings:

1. **Complete history taking** :-Name, age, sex, history of smoking, history of chest

symptoms(cough, expectoration, dyspnea, and wheezes), history of previous intubation and or ventilator support.

2. Complete physical examination including:-

The level of consciousness is determined using a scale called the Glasgow Coma Scale (GCS). Blood pressure is measured in millimeters of Mercury (mmHg), heart rate is measured in beats per minute, surface temperature is measured in degrees centigrade, and oxygen saturation is measured as a percentage. Other important measurements include peak inspiratory pressure (PIP), ventilation rate, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FiO₂). Additionally, doctors listen to a patient's chest to detect any abnormal sounds (auscultatory chest findings).

3. Routine laboratory investigations including:-

Complete blood count (CBC) ·Liver functions test ·Kidney functions test ·Thyroid function tests (free T3, free T4, TSH)·Arterial blood gases (ABG), Random blood sugar ,Coagulation profile, Serum electrolytes Sampling: (Sodium (Na),Potassium (K),Phosphorus (PO₄),Calcium (Ca)).

4. Radiological investigations:

- **Chest x-ray (posterior -antero view)** It shows lung hyperinflation
- **Ct chest :** It shows emphysematous bullae
- **Echo and pelvi abdominal ultrasonography** if needed

5. treatment and follow up

- All enrolled patients received their standard treatment. The protocol of treatment based on GOLD global strategy for the diagnosis, management, and prevention of COPD
- Data related to MV:
 - Monitoring of the last mechanical ventilatory settings and weaning parameters (P0.1, Pimax, RSBI, FiO₂, Pao₂/Fio₂).
 - Duration of MV before weaning.
- All enrolled patients were followed up during the study time (ICU stay).
- Amount of endotracheal secretions which is graded as mild, moderate, and abundant described by a single observer.

Preparation

To make it simpler: A patient needs a special tube to help them breathe better, and they need to start getting better before we can remove the tube.

Technique

When the patient was prepared to start the process of reducing reliance on the ventilator, it needed to be set up correctly. The factors that are measured include the amount of air you

breathe in and out, how fast you breathe, the pressure in your lungs when you exhale, the amount of oxygen you breathe in, and, if applicable, the pressure that helps you breathe. After starting the use of a ventilator machine, it was recommended to get a blood test to check the levels of gases in the blood within 60 minutes. Based on the results, the ventilator's settings could be adjusted.

6- Measuring outcomes

- **The primary outcome in all patients was duration of mechanical ventilation.**
- **The secondary outcomes were ICU length of stay**

Ethical Consideration

The data that were obtained from participants are confidential. The study participants will not be identified by name in any report or publication concerning this study. Before the participants were admitted in this study, the purpose and nature of the study, as well as the risk-benefit assessment was explained to them. An informed consent was obtained.

Statistical analysis design

We looked at the data we gathered and coded it by hand. The computer analyzed the numerical codes using a program called SPSS 22. The data was presented as average and spread for quantitative data, and as numbers and percentages for qualitative data. Different groups were compared using the Chi square-test for qualitative data and the Student's "t" test for quantitative data from two separate samples. The relationship between variables was studied using the correlation coefficient called Pearson correlation. Receiver operating characteristic curves (ROC) were used to find out how well serum phosphate levels could predict the success of weaning, including sensitivity, specificity, and the best cut-off points. Sensitivity means the number of true positive cases divided by the sum of true positive and false negative cases. Specificity, which measures how accurately a test identifies negative results, is calculated by dividing the number of true negatives by the sum of true negatives and false positives. The coefficient interval was determined to be 95%. The importance level was calculated based on the probability values (P). It was determined that a probability value of less than 0. 05 is considered as statistically significant.

RESULTS

Patients with normal phosphate have statistically significantly higher age and BMI than those with hypophosphatemia (**table1**). Patients with hypophosphatemia have statistically significant higher rate of difficult weaning and longer duration of mechanical ventilation than those with normal phosphate (**table2**).There is no statistically significant difference between other vital data of patients with and without hypophosphatemia(**table3**).There is no statistically significant difference in hematological data of patients with and without hypophosphatemia (**table4**). There is no statistically significant difference between ABG data of patients with and without hypophosphatemia (**table5**). There is no statistically significant difference in

biochemical data of patients with and without hypophosphatemia (**table6**). There is no statistically significant difference in serum electrolytes level of patients with and without hypophosphatemia (**table7**) . at cut off level of <3.05, serum phosphate had sensitivity of 82.1% and specificity of 81.8% for predicting difficult weaning from MV (**table8**).

Discussion

The goal of this study was to determine if the level of phosphorus in the blood can help predict when COPD patients with acute exacerbation can stop using a ventilator.

The study involved **70** patients with AECOPD. These patients were divided into two groups based on their initial level of phosphorus when they were admitted. 66% of patients had low levels of phosphorus in their blood, while 34% had normal levels.

In the beginning, research showed that low levels of phosphorus were always found soon after putting COPD patients on mechanical ventilation (MV). This was likely because the body was moving phosphorus inside the cells to balance the acidity in the respiratory system.

This study agrees with the research done by **El-Sayed et al. (2017)**, found that 60% of the AECOPD patients in the study had low levels of phosphorus.

Also agreed with **Fiaccadori and colleagues (1990)** studied phosphorus levels in the blood, how much phosphorus was eaten in the diet, and how the kidneys handled phosphorus in 158 people with COPD. They also looked at the amount of phosphorus in leg muscles of 14 of those patients by taking a small sample of muscle from the thigh using a needle. Hypophosphatemia was found in 21. 5% of those people. These studies found that a lot of people with COPD have low levels of phosphate in their bodies. This is partly due to the medications they take, which affect how their kidneys reabsorb phosphate. Additionally, it also indicates that in people with COPD, the amount of phosphorus in their muscles is likely to be lower when they have low levels of phosphorus in their blood. In this research, when looking at the basic information, the average age of all the patients was 60 years old. 62.8% of the patients were men, while only 37. 2% were women, There were no major differences between the two groups in terms of gender or age. All of the patients were smokers, and there was no noticeable difference between the two groups when it came to their smoking history.

In the past, men have had more cases of COPD compared to women. This difference is believed to be mainly because people who smoke more or work with harmful chemicals are exposed to them more. Recent surveys suggest that the number of people with COPD is becoming more evenly divided between men and women.

This study agreed with **Elsayed et al. (2017)** found that out of all the patients, 90% were men and only 10% were women. The average age of the patients was 67 years old. Also, all the patients in the study were heavy smokers who had smoked for a long time.

Also agreed with **Pauwels and his colleagues. In 2001**, a study discovered that 60% of the patients admitted with AECOPD were males and 40% were females. These patients were also older in age and had been smoking for a long time.

Also agreed with **Farah and her colleagues**. A study in **2013** showed that more than 70% of the patients were men and their average age was 66. 6 years

In this study, the average vital signs of all patients did not show a significant difference. The heart rate was 108 beats per minute in group I and 101 beats per minute in group II. The respiratory rate was 27 cycles per minute in group I and 26 cycles per minute in group II. The temperature was 39 degrees Celsius in both groups. The mean arterial pressure was 88. 7 mmHg in group I and 90. 7 mmHg in group II. The oxygen saturation was 81% in group I and 83% in group II when breathing regular air.

This study agreed with **Elsayed et al.** wrote this. In a study conducted in **2017**, researchers found that there was no significant difference in important data among all patients. In group I, the heart rate was measured to be 105 beats per minute, while in group II it was 100 beats per minute. The respiratory rate in group I was 23 cycles per minute, and in group II it was 20 cycles per minute. The body temperature in group I was 38 degrees Celsius, whereas in group II it was 38. 5 degrees Celsius. The mean arterial pressure in group I was 87 mmHg, while in group II it was 90 mmHg. The oxygen saturation level in group I was 83%, and in group II it was 85% when breathing normally in a regular room environment.

Also agreed with **Farah and her colleagues** In a study in **2013**, researchers looked at important information from all patients. They found that there was no big difference between the two groups. In group I, the average heart rate was 110 beats per minute, while in group II it was 105 beats per minute. The breathing rate was 25 cycles per minute in group I and 23 cycles per minute in group II. The body temperature was 38. 2 degrees Celsius in group I and 38. 6 degrees Celsius in group II. The mean arterial pressure was 85 mmHg in group I and 92 mmHg in group II. The oxygen saturation level in group I was 80% and in group II it was 82% while breathing normal air in the room.

Also agreed with **Zhao et al. (2016)** study , found that mean vital data of all patients had no statistically significant difference, HR:100 b/min in group I ,and 95 b/min in group II ,RR: 22 cycle/min in group I ,and 20 cycle/min in group II , Temp: 38.5 in group I ,and 39 in group II , MAP: 80 mmhg in group I , and 88 mmhg in group II , O2 sat 80% in group I ,and 82% in group II on Room air.

In this study the mean hematological data of all patients had no statistically significant difference ,HB 12.7 g/dl in group I ,and 13.4 g/dl in group II (P=0.087) ,HCT 37.7 in group I ,and 38 in group II (P=0.655) ,WBCS 18.6 x10³/mm³ in group I ,and 19.2 x10³/mm³ in group II (P=0.152) ,PLT 403 x10³/mm³ in group I ,and 407 x10³/mm³ in group II (P=0.583).

This study agreed with **Mair et al. (2009)**, found that the mean hematological data of all patients had no statistically significant difference, HB 12.2 g/dl in group I, and 13 g/dl in group II, HCT 39 in group I, and 40 in group II, WBCS 16.6 x10³/mm³ in group I, and 17.2 x10³/mm³ in group II, PLT 370 x10³/mm³ in group I, and 379 x10³/mm³ in group II.

Also agree with **Zhao et al. (2016)** study, found that the mean hematological data of all patients had no statistically significant difference, HB 11.7 g/dl in group I, and 12.4 g/dl in group II, HCT 42 in group I, and 44 in group II, WBCS 19 x10³/mm³ in group I, and 20.1 x10³/mm³ in group II, PLT 385 x10³/mm³ in group I, and 377 x10³/mm³ in group II.

Also agreed with **Elsayed et al. (2017)** study, found that the mean hematological data of all patients had no statistically significant difference, HB 15g/dl in group I, and 14.6 g/dl in group II, HCT 45 in group I, and 42.5 in group II, WBCS 17 x10³/mm³ in group I, and 15 x10³/mm³ in group II, PLT 420 x10³/mm³ in group I, and 409 x10³/mm³ in group II.

In this study the mean ABG data of all patients had no statistically significant difference, group I (PH 7.1, PCO₂ 85, HCO₃ 30), group II (PH 7.0, PCO₂ 90, HCO₃ 32).

This study agreed with **Elsayed et al. (2017)** study, found that the mean ABG data of all patients had no statistically significant difference, group I (PH 7.2, PCO₂ 75, HCO₃ 29), group II (PH 7.15, PCO₂ 80, HCO₃ 30).

Also agreed with **Farah et al. (2013)** study, found that the mean ABG data of all patients had no statistically, HCO₃ 35), group II (PH 7.0, PCO₂ 90, HCO₃ 32).

Also agreed with **Mair et al. (2009)**, found that the mean ABG data of all patients had no statistically significant difference, group I (PH 7.15, PCO₂ 75, HCO₃ 28), group II (PH 7.2, PCO₂ 70, HCO₃ 29).

In this study the mean biochemical data of all patients had no statistically significant difference, group I blood urea 38.5 mg/dl, and group II 34.7 mg/dl (p=0.025), group I creatinine 1.11 mg/dl, and group II 0.94 mg/dl (p=0.064).

Also agreed with **Elsayed et al. (2017)** study, found that the mean biochemical data of all patients had no statistically significant difference, group I blood urea 40 mg/dl, and group II 35mg/dl, group I creatinine 1.2 mg/dl, and group II 1 mg/dl.

Also agreed with **Zhao et al. (2016)** study, found that the mean biochemical data of all patients had no statistically significant difference, group I blood urea 25 mg/dl, and group II 30 mg/dl, group I creatinine 1 mg/dl, and group II 0.9 mg/dl.

Also agreed with **Farah et al. (2013)** study, found that the mean biochemical data of all patients had no statistically significant difference, group I blood urea 45 mg/dl, and group II 35 mg/dl, group I creatinine 1.3 mg/dl, and group II 1.15 mg/dl.

In this study, the mean of sodium levels (Na) of all patients was 137 mEq/L. The median of Na levels was

lower in low phosphorus group (136) than in normal phosphorus group (139) with no statistically significant difference (p=0.027). The mean of potassium levels (K) of all patients was (4) mEq/L. The median of K values was lower in low phosphorus group (3.6) than in normal phosphorus group (3.9) with statistically significant difference (p=0.803). The mean of Calcium levels (Ca) of all patients was 8 mEq/L. The median of Ca levels was higher in low phosphorus group (8.4) than in normal phosphorus group (7.8) with no statistically significant difference (p=0.136).

In contrast to these findings, **Elsayed et al. (2017)** found that the combination between hypophosphatemia and hypokalemia had significant unfavorable outcome (p= 0.03).

Also, **Mair et al. (2009)** found that the combination between hypophosphatemia and hypokalemia increased the need for ventilation and duration of ventilation. These differences may be due to small sample size and different selection criteria, non-mechanically ventilated patients were enrolled in these studies.

In this study, the mean of MV duration of all patients was 6 days. Low phosphorus group showed a statistically significant longer duration of MV than normal phosphorus group (median, 8 Vs 3, p<0.0001). difficult weaning in low phosphorus group was (78.26%) vs (29.16%) in normal phosphorus group (p<0.0001). These results may show that hypophosphatemia causes respiratory muscular weakness (a decrease in the volume of autonomous respiration), reduction of static lung compliance and a loss of respiratory function, leading to weaning failure.

After univariate analysis, phosphorus level showed fair statistically significant downhill correlation with the duration of MV in all enrolled patients (r= -0.497, p <0.0001).

This study agreed with **El-Sayed et al. (2017)**, studied 50 patients with AECOPD admitted to chest department and respiratory ICU at Benha University hospital in the period between October 2014 and March 2015. A comparison was made between low phosphorus (<2.5 mg/dl) group and normal blood phosphorus (2.5–4.5 mg/dl) group. The duration of MV (days) was significantly higher in low phosphorus group (6.23 ± 4.982) than normal phosphorus group (4.40 ± 2.011) (p= 0.04).

Also agreed with **Zhao et al. (2016)**, retrospectively analyzed the medical records of 67 AECOPD cases, treated with MV between 2011 and 2013. The patients were assigned to the hypophosphatemic and the normophosphatemic groups according to their serum phosphate levels (with the threshold of 0.87 mmol/l). A significantly higher percentage of failure-to-wean from MV was observed in the hypophosphatemia group vs. the normophosphatemic group (34.21 vs. 10.34%, p<0.05). Furthermore, hypophosphatemia was associated with respiratory muscular weakness.

Also agreed with **Yueqing et al. (1997)** study, found that ventilatory function improved after phosphate supplementation in the patients with severe

hypophosphatemia. Regarding this study limitations, small sample size design was a main limitation. Risk factors for hypophosphatemia were not studied. Fibroblast Growth Factor 23 (FGF-23) was not studied although it has been shown to play an important role in the regulation of body phosphate. The only primary outcome of this study was the duration of MV. Respiratory parameters such as tidal volume of spontaneous respiration, the minute ventilation volume and static lung compliance were not studied.

CONCLUSION

In the light of the previous results, hypophosphatemia (Ph <2.5 mg/dL) was associated with poor prognosis in terms of longer durations of mechanical ventilations in patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Hypophosphatemia should be included in initial assessment of such patients to stratify them.

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Results Tables

Table 1 : Comparison of demographic data of the studied population

		Normal phosphate	Hypophosphatemia	Independent student T test	
		N=24	N=46	t	p-value
Age years	Range	56-73	45-73	3.4678	0.0009
	Mean ± SD	65.41 ± 5.14	59.15 ± 8.01		
BMI	Range	22-44	18-45	2.2607	0.0270
	Mean ± SD	34.54 ± 7.28	30.77 ± 6.26		
Sex	Male	18 (75%)	26 (56.52%)	2.306	0.128
	Female	6(25%)	20 (43.47 %)		
Smoking	Yes	24 (100%)	46 (100%)	-	1
	No	0	0		

Table 2 : Comparison of weaning of the studied population

		Normal phosphate	Hypophosphatemia	chi-square test	
		N=24	N=46		
		N (%)	N (%)	t/X2	p-value
Weaning	Easy	17 (70.83%)	10 (21.73%)	16.043	<0.0001
	Difficult	7 (29.16%)	36 (78.26%)		
Duration of MV (days)	Range	2 – 5	5 – 9	19.341	<0.0001
	Mean ± SD	3.424 ± 1.032	8.118 ± 0.927		

Table 3: Comparison of vital data of the studied population

Baseline	Normal phosphate			Hypophosphatemia			Independent student T test	
	N=24			N=46				
	mean	±	SD	mean	±	SD	t	p-value
HR (beat/min)	108.00	±	12.22	101.64	±	7.71	2.664	0.0096

RR (cycle/min)	27.65	±	3.08	26.48	±	1.82	1.9994	0.0496
Temperature °C	39.06	±	0.17	39.06	±	0.17	0	1.0
SBP (mmHg)	140.74	±	13.70	137.94	±	13.45	0.821	0.414
DBP (mmHg)	82.06	±	9.36	82.27	±	7.40	0.102	0.918
MBP (mmHg)	88.71	±	7.30	90.73	±	6.63	1.168	0.246
O2 saturation %	81.24	±	5.38	83.09	±	4.66	1.4947	0.1396

Table 4: Comparison of hematological data of the studied population

	Normal phosphate			Hypophosphatemia			Independent student T test	
	N=24			N=46				
	mean	±	SD	mean	±	SD	t	p-value
HB (mg/dl)	12.75	±	1.56	13.47	±	1.69	1.735	0.087
HCT	37.77	±	4.24	38.12	±	2.32	0.447	0.655
WBCs x10 ³ /mm ³	18.62	±	1.56	19.22	±	1.69	1.446	0.152
Platelet x10 ³ /mm ³	403.88	±	21.18	407.27	±	25.96	0.550	0.583

Table 5: Comparison of ABG data of the studied population

	Normal phosphate			Hypophosphatemia			Independent student T test	
	N=24			N=46				
	mean	±	SD	mean	±	SD	T	p-value
PH	7.1	±	0.01	7.0	±	0.04	1.201	0.2338
PCO2	85	±	8.14	90	±	5.64	3.012	0.0036
PO2	54.62	±	21.93	53.67	±	9.43	0.253	0.800
HCO2	30	±	4.57	32	±	3.11	1.082	0.2830
BE	-6.718	±	3.985	-7.607	±	4.192	0.856	0.394

Table 6: Comparison of biochemical data of the studied population

	Normal phosphate			Hypophosphatemia			Independent student T test	
	N=24			N=46			T	p-value
	mean	±	SD	mean	±	SD		
Albumin mg/dl	3.83	±	0.44	3.98	±	0.44	1.353	0.180
CRP mg/dl	35.82	±	25.39	27.84	±	24.53	1.276	0.206
Urea mg/dl	38.53	±	7.32	34.70	±	6.27	2.289	0.025
Creatinine mg/dl	1.11	±	0.41	0.94	±	0.33	1.880	0.064

Table 7: Comparison of serum electrolytes level of the studied population

	Normal phosphate			Hypophosphatemia			Independent student T test	
	N=24			N=46			T	p-value
	mean	±	SD	mean	±	SD		
Na mg/dl	139.29	±	5.21	136.21	±	5.51	2.260	0.027
Ca mg/dl	7.80	±	1.64	8.43	±	1.67	1.507	0.136
K mg/dl	3.77	±	0.70	3.73	±	0.60	0.249	0.803

Table 8: Sensitivity, specificity and cut off value of serum phosphate for prediction of difficult weaning

Cut off point	Area under curve	Std. Error	sensitivity %	specificity %	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
<3.05	0.935	0.045	82.10%	81.80%	0.847	1.000