Association of Hypophosphatemia with Failure-to-Wean from Mechanical Ventilation

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Abstract. Severe hypophosphatemia is known to be associated with respiratory failure, but there are few studies that specifically examine the relationship between serum phosphorus concentration and failure to wean patients from mechanical ventilation. This study investigated the association between hypophosphatemia and weaning failure in patients in two medical intensive care units (ICU). The study was conducted in a prospectively developed cohort of 66 patients being treated with ventilatory support and in whom 193 weaning trials were attempted. Ultimately, all 66 subjects were successfully weaned. A cross-sectional analysis was conducted on serum phosphorus levels and success or failure to wean the patients from ventilators. At the time of the successful weaning attempts (n = 66), the subjects’ serum phosphorus concentrations (mean ± SD) were 1.18 ± 0.27 mmol/L, whereas at all failed weaning attempts (n = 127) serum phosphorus concentrations averaged 1.06 ± 0.31 mmol/L (p = 0.008). Subjects with phosphorus concentrations below the reference interval (RI) in our laboratory (<0.80 mmol/L) had greater risk for weaning failure compared to subjects with phosphorus concentrations at or above the RI (relative risk = 1.18; 95% confidence interval = 1.06 to 1.32; p = 0.01). Serum calcium concentrations were not significantly different at the time of successful weaning compared to those at failed weaning attempts. This study indicates that there is an association between hypophosphatemia and failure-to-wean from mechanical ventilation in ICU patients on ventilatory support.

Keywords: hypophosphatemia, mechanical ventilation, respiratory failure

Introduction

Maintenance of a normal serum phosphorus level is vital for cellular function [1]. Hypophosphatemia affects approximately 2.2-3.1% of hospitalized patients and 28-33% of patients admitted to an ICU [2]. The most common clinical manifestation of phosphorus deficiency is weakness of skeletal or smooth muscle; however rhabdomyolysis, impaired cardiac contractility, and hemolytic anemia are also manifestations of hypophosphatemia [3].

Hypophosphatemia can cause acute respiratory failure and it impairs diaphragmatic contractility [4]. Although hypophosphatemia has been studied as a cause of respiratory failure [5-11], to our knowledge, the effect of serum phosphorus level on weaning from mechanical ventilation has only been suggested by relatively infrequent case reports. This prospective observational study was conducted to determine if patients with low serum phosphorus levels are at increased risk for failure-to-wean from ventilatory support.

Subjects and Methods

Setting. The study was conducted at two urban teaching hospitals in the northeastern United States that are core
affiliates of the School of Health and Medical Sciences of Seton Hall University. The protocol was approved by the Institutional Review Boards (IRB) of St. Michael’s Medical Center (Newark, NJ) and Trinitas Regional Medical Center (Elizabeth, NJ). For medically related protocols at its affiliated healthcare institutions, Seton Hall University’s IRB delegates the approval process to the individual facilities at which the studies are performed.

Protocol and patients. This study examined a prospective cohort of 66 consecutive patients on mechanical ventilation admitted to a medical ICU during the 8-mo period from December 2008 to July 2009, inclusive. The inclusion criteria were: patients on ventilatory support above the age of 21 yr who met the criteria for weaning, which includes patients able to breathe spontaneously, who have an adequate cough reflex, respiratory rate <35/min, temperature <101.5°F, no vaso-pressors for blood pressure control, peak end-expiratory pressure <5 cm H2O, oxygen saturation ≥90% with FIO2 (fraction of inspired oxygen) not >60%, rapid shallow breathing index <105, and who are judged to be hemodynamically stable. Patients were excluded who did not meet these criteria or who had end-stage renal disease (GFR <15 ml/min). Baseline demographic data, diagnoses, and the indications for mechanical ventilation were collected, as well as serum phosphorus and Ca²⁺ concentrations and weaning outcomes (failure/success). The weaning trials were conducted using pressure support ventilation (PSV). Phosphorus and calcium were determined in serum samples obtained on the morning of the weaning trial.

Laboratory methods. Serum phosphorous and calcium were determined with a Synchron LX automated analyzer (Beckman Coulter, Fullerton, CA) using reagents supplied by the manufacturer. Serum total calcium was corrected for serum albumin concentration, assayed simultaneously. The reference interval (RI) for serum phosphorus in our laboratory is 0.80 to 1.53 mmol/L; for serum calcium, the RI is 2.23 to 2.58 mmol/L.

Statistics. For this study, α was set at 0.05, ie, p <0.05 (two-sided) was statistically significant. The distributions of interval data (age, serum phosphorus, serum calcium) were tested for normality by the D’Agostino-Pearson omnibus normality test. Because normal distributions were not observed throughout, non-parametric analyses were used. The Mann-Whitney test was used for two-group comparisons and the Kruskal-Wallis test followed by Dunn’s post hoc test was used for comparisons of >2 groups. Trend analysis was done using Cuzick’s rank test [12]. Data were expressed as medians and interquartile ranges (IQR). Categorical data were analyzed in contingency table format and p-values were obtained by Fisher’s exact test; because the study was conducted prospectively, relative risk (RR) was used as the measure of clinical relevance and is reported along with lower and upper 95% confidence intervals (CI). Receiver-operating-characteristic (ROC) curve analysis was used to establish a cut-off for serum phosphorus in predicting weaning success. Statistical analyses (other than Cuzick’s test) were done using Prism v.5 software (GraphPad, San Diego, CA) on a personal computer. Cuzick’s test results were computed manually.

Results

A total of 66 patients were enrolled in this study (35 male and 31 female). Of those, 14 patients (21.2%) developed hypophosphatemia (defined as a value below the lower limit of the RI) during at least one of their weaning trials; the other 52 subjects had either normal or slightly elevated

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with hypophosphatemia (n = 14)</th>
<th>Patients with normal or high serum phosphorus (n = 52)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Age (yr, median, IQR)</td>
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<td>65 (54-79)</td>
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<td>Gender</td>
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<td>Indication for ventilation</td>
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<td></td>
</tr>
<tr>
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<td>2 (14%)</td>
<td>5 (10%)</td>
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<tr>
<td>asthma</td>
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<td>6 (11%)</td>
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<tr>
<td>congestive heart failure</td>
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<td>8 (15%)</td>
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<td>7 (13%)</td>
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</tr>
<tr>
<td>other</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
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</tbody>
</table>

COPD = chronic obstructive pulmonary disease
NA = not applicable
ARDS = acute respiratory disease syndrome

Table 1. Baseline characteristics of subjects in the study. The two groups are based on serum phosphorus levels at the time of weaning. Because of the number of categories, no attempt was made to test if differences between the two groups with regard to indication are statistically significant. Some patients had >1 co-morbidity, while others were admitted for acute conditions (eg, drug overdose, sepsis) or were post-operative.

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serum phosphorus concentrations for all weaning attempts. The baseline characteristics for both of these groups are shown in Table 1.

A total of 193 weaning trials were conducted on these patients. Ultimately, all 66 subjects were successfully weaned. Overall, at the time of successful weaning, the subjects’ mean serum phosphorus concentration was 1.18 ± 0.27 mmol/L, whereas at the time of failed weaning attempts (n = 127) serum phosphorus concentrations averaged 1.06 ± 0.31 mmol/L (p = 0.008). Total serum calcium concentrations, obtained simultaneously with phosphorus, were nearly identical for the two groups (successfully weaned: 2.34 ± 0.15 mmol/L; failed: 2.34 ± 0.16; p = 0.86). When the patients were hypophosphatemic, the number of failed weaning trials was 26 and the number of successful weaning trials was 4. When the patients had normal or high serum phosphorus levels, based on the RI, the number of failed weaning trials was 101 and the number of successful trials was 62. (RR = 1.18; 95% CI: 1.06 to 1.32; p = 0.011).

The data were analyzed using a ROC curve to determine the optimum cut-off for serum phosphorus as a predictor of weaning success or failure (Fig. 1). The area under the curve (AUC) of 0.61 suggests that the association of phosphorus levels with weaning success, though statistically significant (p = 0.012), is not particularly strong. The cut-off determined from the ROC curve was 1.05 mmol/L, roughly in the middle of the laboratory RI. We examined the issue of weaning failure and found that at the time of successful weaning (extubation), 48 of 66 (72.7%) subjects had serum phosphorus levels above the cut-off, while for failed weaning trials, ie, extubation not accomplished, 70 of 127 (55%) trials were associated with serum phosphorus levels below 1.05 mmol/L (RR = 1.62; 95% CI: 1.27 to 2.07; p = 0.0002).

There were 16 subjects who required 4 weaning trials prior to finally being weaned. We examined phosphorus concentrations during each of these trials to determine if successive approaches toward a presumably adequate phosphorus level would be observed in these subjects. These data are shown in Fig. 2. As the subjects proceeded toward a successful outcome, the median values of serum phosphorus demonstrated significant (p <0.001) incremental increases. Overall, there was a significant (p = 0.012) difference among the values, with the first weaning attempt and the successful weaning also a significantly different pair (p <0.05, post hoc).

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**Fig. 1.** ROC curve for association of serum phosphorus with successful weaning from mechanical ventilation. Cut-off at 1.05 mmol/L is shown.

**Fig. 2.** Serum phosphorus for 16 subjects who required 4 weaning trials prior to successfully being weaned. Overall differences between the groups were statistically significant (p = 0.012) with a significant difference (p < 0.05, by Dunn’s post hoc test) between the first attempt and the successful attempt. The increasing trend, indicated by the dotted trend line, was also significant (p < 0.01).
Discussion

Weaning from mechanical ventilation includes the entire process of withdrawing ventilator support and removal of the endotracheal tube. Only after the underlying pathophysiology necessitating mechanical ventilation is resolved, can the weaning process be initiated [13].

Hypophosphatemia and other electrolyte abnormalities can cause respiratory failure, but there are few studies that specifically evaluate the relative contribution of each of these metabolic derangements to weaning failure [14]. Respiratory insufficiency and failure-to-wean may well be due to inadequate 2,3-diphosphoglycerate production causing a shift in the hemoglobin dissociation curve to the left. Additionally, the respiratory muscles may be weakened by inadequate production of phosphorylated intermediates such as ATP or creatine phosphate [15] and diaphragmatic contractility may be impaired during the hypophosphatemic state [4].

Gravelyn and colleagues [16] studied 23 hospitalized patients with low serum phosphate level (<0.80 mmol/L) and performed bedside measurements of maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). The mean initial MIP and MEP values were significantly lower for the hypophosphatemic subjects compared to controls. There have been several case reports that showed a relationship between hypophosphatemia and respiratory failure, as well as recurrent weaning failure, in the absence of underlying pulmonary diseases [5-11], but we have not found any studies that specifically addressed the effect of low serum phosphorus levels on failure-to-wean from ventilatory support.

The data presented herein emanate from a prospectively conducted, cross-sectional analysis of 66 patients who underwent nearly two hundred weaning trials. Our data demonstrate significantly lower serum phosphorus concentrations in subjects who failed the weaning process. Our data suggest that if the serum phosphorus concentration is <1.05 mmol/L, there is 18% greater risk of failure-to-wean from mechanical ventilation. Our data also suggest that, in successive weaning trials in subjects who failed their first weaning attempt, phosphorus levels increased until they were adequate to effect a successful outcome. It is important to recognize that this effect does not appear related to secondary alterations in serum calcium; indeed, the serum calcium concentrations were remarkably similar.

In a study such as this, even though prospectively conducted, there are many factors associated with weaning failure that are impossible to control. We caution strongly against inferring a causal role for hypophosphatemia in situations where patients are unable to be weaned from ventilator support. However, Aubier et al [4] performed a quasi-experimental (non-randomized) study of 8 subjects with hypophosphatemia that documented changes in physiologic parameters (eg, diaphragmatic contractility) associated with hypophosphatemia. Their data suggest a physiologic mechanism that might explain the weaning failure we observed.

In conclusion, this study supports the importance of adequate serum phosphorus levels in maintaining the strength of the musculature responsible for ventilation and it addresses the specific issue of weaning patients from mechanical respirators. Our results clearly suggest that in a cohort of ICU patients drawn from two teaching hospitals, adequate serum phosphorus levels are associated with successful weaning from ventilation.

References