Persistent, progressive hypophosphataemia after voluntary hyperventilation

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ABSTRACT

Hyperventilation (HV) and respiratory alkalosis are associated with hypophosphataemia, although the extent and duration of HV required to produce changes in serum phosphate levels are not known. We sought to characterize the effects of HV, with or without dextrose loading, on serum phosphate levels and other biochemical parameters. HV was monitored by controlling the end-tidal partial pressure of carbon dioxide ($P_{ETCO_2}$). The effect of dextrose was studied because infusion of a glucose load is known to promote a fall in serum phosphate via stimulation of glycolysis. Eight healthy volunteers were enrolled in four study protocols: (1) HV for 20 min to a $P_{ETCO_2}$ of 25–30 mmHg (mild); (2) HV for 20 min to a $P_{ETCO_2}$ of 15–20 mmHg (severe); (3) mild HV with intravenous dextrose loading, and (4) dextrose loading alone. Periodic measurements of serum phosphate, venous pH, serum 2,3-diphosphoglycerate (2,3-DPG) and other parameters were made. Serum phosphate fell during HV and continued to decline after cessation of HV. Dextrose loading alone caused a fall in serum phosphate that continued for at least 30 min after cessation of the infusion ($P < 0.0002$). HV combined with dextrose resulted in a greater decline in serum phosphate than either variable alone ($P = 0.003$). The maximal decline in serum phosphate occurred in severe HV, with a mean decrease of 0.38 mmol/l at 20 min after cessation of HV ($P < 0.0001$). Serum phosphate was still significantly lowered compared with baseline at 90 min after cessation of HV ($P = 0.001$). Other significant changes seen with HV included a decrease in serum glucose ($P < 0.01$), a decrease in serum potassium ($P < 0.05$) and an increase in venous pH ($P < 0.007$). Serum 2,3-DPG levels did not change significantly in any study protocol. Thus relatively mild acute HV produces significant changes in serum phosphate. In both mild and severe HV this effect is progressive after cessation of HV. This phenomenon has not been shown before, and may have significant clinical implications.

INTRODUCTION

Hyperventilation (HV) is known to cause a variety of physiological changes in humans. Many studies of HV have examined the associated changes in blood gas concentrations [1,2], while others have focused on red blood cell and plasma biochemical changes [2–5]. Decreases in total calcium, ionized magnesium, phosphate and potassium have been reported in association with prolonged HV [3,4,6]. Marked hypophosphataemia may cause a variety of clinical disorders, including respiratory muscle weakness [7,8], central nervous system dysfunction, rhabdomyolysis, cardiac dysfunction [7–9] and altered haemoglobin oxygen affinity [10]. Changes in blood phosphate levels in association with HV and respiratory alkalosis have been recognized for many years [4]. This is a common cause of hypophosphataemia in hospitalized patients [9] and is purported to result from an intracellular shift of phosphate [4] with increased phosphofructokinase activity.

Key words: 2,3-diphosphoglycerate, hyperventilation, phosphate.

Abbreviations: 2,3-DPG, 2,3-diphosphoglycerate; GEE, Generalized Estimating Equation; HV, hyperventilation; $P_{ETCO_2}$, end-tidal partial pressure of carbon dioxide.

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due to a rise in intracellular pH [9]. The effect upon serum phosphate of differing degrees of HV is not known. We aimed to determine the alterations in phosphate levels that occur with varying degrees of HV in healthy adults, as well as the time course of resolution of these changes.

We also sought to determine whether there were changes in 2,3-diphosphoglycerate (2,3-DPG) levels during short-term mild and severe HV. Alterations in 2,3-DPG may have considerable clinical significance via an effect on haemoglobin oxygen affinity and therefore tissue oxygen transport [11]. Chronic hypophosphataemia has been associated with depletion of red blood cell organic phosphates, including 2,3-DPG [10,12–14]. Conversely, intracellular alkalosis (as develops with HV) may induce an increase in the red cell 2,3-DPG concentration [15]. In the one study [12] that examined the effect of acute HV on 2,3-DPG levels, no significant change was noted. This study, however, did not quantify the degree of hypocapnia, and thus the effect of acute HV on serum 2,3-DPG remains unclear.

Acute glucose administration has been shown experimentally to accentuate the hypophosphataemia associated with respiratory alkalosis [16]. Glucose administration and the associated insulin release stimulate glycolysis, the phosphorylation of glucose compounds and the intracellular shift of phosphorus [16,17]. We sought to characterize this effect accurately in human subjects. The present study therefore aimed to accurately measure degrees of acute HV and the time course of subsequent biochemical changes, with particular reference to serum phosphate.

METHODS

Experimental design

Eight healthy adults (seven males and one female) volunteered to participate in the study, and informed written consent was obtained. The mean age of the participants was 33 years (range 26–46 years) and their mean weight was 77 kg (52–100 kg). The Ethics Committee of Manly Hospital approved the study.

There were four HV protocols. (1) Mild HV. HV to an end-tidal partial pressure of CO\textsubscript{2} (\textit{PETCO}_2) of 25–30 mmHg for 20 min, with a further 30 min of observation post-HV. (2) Severe HV. HV to a \textit{PETCO}_2 of 15–20 mmHg for 20 min, with a further 90 min of observation post-HV. (3) Mild HV plus intravenous dextrose. HV to a \textit{PETCO}_2 of 25–30 mmHg for 20 min, with an intravenous infusion of 500 ml of 5% (w/v) dextrose over 30 min (beginning 10 min before the onset of HV), with a further 30 min of observation post HV. The potentiating hypophosphataemic effect of intravenous dextrose administration was studied with mild HV only, as it was felt that once established this would represent the phenomenon with all grades of HV. (4) Dextrose alone. Intravenous infusion of 500 ml of 5% (w/v) dextrose over 30 min without HV, with a further 30 min of observation after this period.

Each arm of the study was undertaken on a separate day. Subjects fasted for at least 4 h before beginning each protocol. For Protocols 1 and 2, an 18-gauge cannula was placed in a cubital fossa vein, from which blood was withdrawn for analysis. For Protocols 3 and 4 an additional 20-gauge cannula was placed at a convenient site in the other arm for infusion of dextrose.

After placement of intravenous cannulae, subjects rested in a semi-recumbent position for the duration of the study protocol. Baseline blood samples were taken and subjects then began hyperventilating through a mouthpiece attached to a sample line from an infrared CO\textsubscript{2} analyser. \textit{PETCO}_2 was measured using a sidearm attached to a mouthpiece, connected to a modular monitoring system (model no. 66S; Hewlett Packard Corp.). The waveform and the digital display of \textit{PETCO}_2 were observed continuously by both the subject and the investigator to ensure that \textit{PETCO}_2 remained below the level required for the specific protocol. After 20 min of HV at the required \textit{PETCO}_2, subjects were then asked to breathe normally and remain resting for the period of time specified in each protocol. Heart rate, blood pressure and oxygen saturation were observed continuously for the duration of the experiment. The greatest level of oxygen desaturation post-HV was recorded.

Venous pH, total calcium, phosphate, magnesium, potassium, chloride, sodium, total protein, albumin and blood glucose were measured in all the samples obtained. All samples were drawn into heparinized tubes. The protocol for sampling of blood is summarized in Figure 1. For Protocol 1 blood was drawn just prior to HV, at 10 and 20 min of HV and at 10, 20 and 30 min after cessation of HV. For Protocol 2 the same procedure was undertaken, and additional samples were taken at 60 and 90 min after cessation of HV. For Protocol 3 a baseline sample was taken prior to the start of the infusion. HV was begun 10 min later, and samples were taken at 10 and 20 min of HV and at 10, 20 and 30 min after cessation of HV. For Protocol 4 a baseline sample was taken prior to the infusion and the timing of further samples was the same as for Protocol 3. 2,3-DPG was determined in three samples from each experiment, for which blood was drawn into heparinized tubes. For Protocols 1–3, samples were taken at the beginning and at the end of HV and 20 min after cessation of HV. For Protocol 4 samples were taken prior to and at the end of the infusion and 20 min after ceasing the infusion.

Analytical procedures

All measurements were performed in duplicate. Serum sodium, potassium and chloride were measured using ion-sensitive electrodes. Serum phosphate was deter-
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Figure 1  Study protocol flow chart

ETCO₂ = PETCO₂.

Statistical analyses

Statistical analyses and graphs were carried out using Microsoft Excel (Microsoft Corp.) and SAS statistical software (SAS Institute, Inc., Cary, NC, U.S.A.). In the initial analysis a series of paired t-tests was used to compare changes in the baseline levels of serum phosphate and other biochemical parameters with subsequent values. A second, more sophisticated, analysis using Generalized Estimating Equations (GEEs) was also undertaken which took into account the longitudinal nature of the data, and the inherent correlation between observations over time within a subject [18a].

The GEE analysis assumed an autoregressive correlation structure (assuming that an unstructured correlation gave very similar results). Time was coded as categorical with baseline as the reference category. Overall the estimates for the t-tests and GEEs were determined by measurement of the absorption of the reduced phosphomolybdate complex at different UV wavelengths. Calcium was measured by a modification of the calcium-o-cresolphthalein complexone to decrease magnesium interference. Magnesium levels were determined by a modification of the Methylthymol Blue complexometric procedure to decrease calcium interference. Total protein was measured by a modified biuret method, and albumin by the Bromocresol Purple dye-binding method. Blood glucose levels were measured by the hexokinase/glucose 6-dehydrogenase method. Venous pH was measured on an ABL30 Blood Gas Analyzer (Radiometer, Copenhagen, Denmark). For 2,3-DPG measurement, 0.5 ml of heparinized blood was transferred to 1.5 ml of 8% trichloroacetic acid and mixed thoroughly. After refrigerating for 5 min to allow complete precipitation, the mixture was centrifuged (2500 rev./min; 10 min). The supernatant was then separated and frozen immediately for subsequent analysis. Analysis was performed using a Sigma Diagnostics kit (Sigma Diagnostics, St. Louis, MO, U.S.A.) based on the method of Lowry et al. [18].

Statistical analyses

Statistical analyses and graphs were carried out using Microsoft Excel (Microsoft Corp.) and SAS statistical software (SAS Institute, Inc., Cary, NC, U.S.A.). In the initial analysis a series of paired t-tests was used to compare changes in the baseline levels of serum phosphate and other biochemical parameters with subsequent values. A second, more sophisticated, analysis using Generalized Estimating Equations (GEEs) was also undertaken which took into account the longitudinal nature of the data, and the inherent correlation between observations over time within a subject [18a].

The GEE analysis assumed an autoregressive correlation structure (assuming that an unstructured correlation gave very similar results). Time was coded as categorical with baseline as the reference category. Overall the estimates for the t-tests and GEEs were
identical, and their standard errors were similar to within 0.01, and all highly significant. Hence, for simplicity, only t-test results are reported.

Finally, an analysis of variance of the areas under the curves of the decline in phosphate levels for Protocols 1, 3 and 4 was used to compare the effects of these protocols. This enabled a more reliable method of examining serial measurements [19]. P values of $< 0.05$ were considered statistically significant. All values are expressed as mean and S.D. Error bars presented in graphs represent S.D.s around the mean values.

RESULTS

Effects of HV

The results with mild and severe HV are shown in Tables 1 and 2. All subjects reported tingling and numbness of the hands of varying intensity during mild HV, which was more marked in severe HV. After severe HV, all of the subjects reported feeling light-headed, and four of the subjects fell asleep in the post-HV phase. The maximum fall in oxygen saturation post-HV after mild HV was to 90% (range 86–92%), and after severe HV to 72% (range 52–83%).

Table 1  Effects of HV to P\textsubscript{ETCO\textsubscript{2}} = 25–30 mmHg (mild HV)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
<th>50 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.04 (0.08)</td>
<td>0.97 (0.06)**</td>
<td>0.91 (0.07)**</td>
<td>0.90 (0.07)**</td>
<td>0.88 (0.07)**</td>
<td>0.88 (0.07)**</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.73 (0.25)</td>
<td>3.73 (0.15)</td>
<td>3.78 (0.25)</td>
<td>3.58 (0.19)*</td>
<td>3.69 (0.15)</td>
<td>3.73 (0.16)</td>
</tr>
<tr>
<td>Total calcium (mmol/l)</td>
<td>2.37 (0.12)</td>
<td>2.39 (0.09)</td>
<td>2.40 (0.09)</td>
<td>2.37 (0.08)</td>
<td>2.38 (0.10)</td>
<td>2.37 (0.09)</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.75 (0.09)</td>
<td>0.71 (0.07)</td>
<td>0.73 (0.07)</td>
<td>0.71 (0.06)</td>
<td>0.76 (0.12)</td>
<td>0.72 (0.04)</td>
</tr>
<tr>
<td>Serum 2,3-DPG (\mu mol/ml)</td>
<td>1.71 (0.36)</td>
<td>–</td>
<td>1.82 (0.28)</td>
<td>–</td>
<td>1.73 (0.34)</td>
<td>–</td>
</tr>
<tr>
<td>Serum glucose (mmol/l)</td>
<td>4.76 (0.57)</td>
<td>4.59 (0.56)**</td>
<td>4.61 (0.58)</td>
<td>4.89 (0.46)</td>
<td>4.99 (0.45)**</td>
<td>5.03 (0.42)*</td>
</tr>
</tbody>
</table>

Mild HV

Results are summarized in Table 1. Venous pH rose from $7.41 \pm 0.02$ at baseline to $7.49 \pm 0.07$ ($P = 0.007$) at the end of HV. Venous pH returned to baseline between 30 and 40 min after cessation of HV. Serum phosphate fell from $1.04 \pm 0.08$ to $0.91 \pm 0.07$ mmol/l ($P < 0.0001$) at completion of HV, and fell further to $0.88 \pm 0.07$ mmol/l at 30 min after cessation of HV ($P < 0.0001$) (the end of the observation period) (Figure 2). Serum potassium did not change during HV, but fell significantly at 10 min after cessation of HV ($P < 0.05$). Glucose fell from $4.76 \pm 0.57$ to $4.59 \pm 0.56$ mmol/l ($P = 0.006$) in the first 10 min of HV, then increased steadily to $5.03 \pm 0.42$ mmol/l ($P < 0.05$) at the end of the observation period. There were no other significant changes.

Severe HV

Results are summarized in Table 2. Venous pH rose from a baseline level of $7.37 \pm 0.03$ to $7.57 \pm 0.06$ at the end of the HV period ($P < 0.0001$), but had returned to normal by 60 min after cessation of HV. Serum phosphate fell from $1.05 \pm 0.08$ to $0.73 \pm 0.11$ mmol/l ($P < 0.0001$) at completion of HV, and reached a minimum value of $0.67 \pm 0.13$ mmol/l ($P < 0.0001$) at 20 min after cessation of HV (Figure 2). Serum phosphate was still significantly

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Table 2  Effects of HV to PetCo2 = 15–20 mmHg (severe HV)
The period of HV lasted from 0 to 20 min. Values are presented as mean (S.D.). Significance of differences compared with baseline: *P < 0.05; **P < 0.01.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
<th>50 min</th>
<th>80 min</th>
<th>110 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate (mmol/l)</td>
<td>1.05</td>
<td>0.91</td>
<td>0.73</td>
<td>0.67</td>
<td>0.67</td>
<td>0.70</td>
<td>0.78</td>
<td>0.90</td>
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<td>(0.08)</td>
<td>(0.09)**</td>
<td>(0.11)**</td>
<td>(0.11)**</td>
<td>(0.13)**</td>
<td>(0.11)**</td>
<td>(0.12)**</td>
<td>(0.10)**</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.76</td>
<td>3.80</td>
<td>3.73</td>
<td>3.41</td>
<td>3.45</td>
<td>3.40</td>
<td>3.63</td>
<td>3.70</td>
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<tr>
<td>(0.13)</td>
<td>(0.09)</td>
<td>(0.10)</td>
<td>(0.12)**</td>
<td>(0.15)**</td>
<td>(0.13)**</td>
<td>(0.14)</td>
<td>(0.15)</td>
<td></td>
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<tr>
<td>Total calcium (mmol/l)</td>
<td>2.34</td>
<td>2.44</td>
<td>2.49</td>
<td>2.42</td>
<td>2.30</td>
<td>2.35</td>
<td>2.33</td>
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<tr>
<td>(0.07)</td>
<td>(0.08)**</td>
<td>(0.09)**</td>
<td>(0.08)**</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.08)</td>
<td>(0.05)</td>
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<tr>
<td>Magnesium (mmol/l)</td>
<td>0.77</td>
<td>0.74</td>
<td>0.76</td>
<td>0.73</td>
<td>0.73</td>
<td>0.71</td>
<td>0.72</td>
<td>0.73</td>
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<td>(0.06)</td>
<td>(0.04)</td>
<td>(0.05)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.07)*</td>
<td>(0.05)*</td>
<td>(0.05)</td>
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<tr>
<td>Serum 2,3-DPG (µmol/ml)</td>
<td>1.92</td>
<td>–</td>
<td>1.93</td>
<td>–</td>
<td>1.82</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>(0.16)</td>
<td>(0.04)</td>
<td>(0.05)</td>
<td>(0.07)</td>
<td>(0.07)</td>
<td>(0.07)*</td>
<td>(0.05)*</td>
<td>(0.05)</td>
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</tr>
<tr>
<td>Serum glucose (mmol/l)</td>
<td>4.68</td>
<td>4.51</td>
<td>4.66</td>
<td>5.13</td>
<td>5.28</td>
<td>5.26</td>
<td>4.86</td>
<td>4.94</td>
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<tr>
<td>(0.58)</td>
<td>(0.62)*</td>
<td>(0.70)</td>
<td>(0.60)**</td>
<td>(0.54)**</td>
<td>(0.43)**</td>
<td>(0.33)</td>
<td>(0.41)*</td>
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</tr>
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</table>

decreased, at 0.90 ± 0.10 mmol/l (P = 0.001), at the end of the follow-up, 90 min after ceasing HV. Significant changes were noted in serum potassium, total calcium and magnesium. As in mild HV, serum potassium fell significantly in the 10 min after ceasing HV (P < 0.0001). It remained significantly lowered until 30 min after cessation of HV. Total serum calcium rose significantly for the period of severe HV, peaking at completion of cessation of HV. Staubli et al. [12] demonstrated a significant fall in serum phosphate after cessation of HV. There was no change in venous pH after the dextrose infusion alone. Serum phosphate had declined significantly by the time of the first measurement (10 min after the start of the infusion), and achieved its lowest level at the end of the observation period, falling from 1.03 ± 0.09 mmol/l to 0.90 ± 0.11 mmol/l (P < 0.0002) (Figure 2). This was not significantly different from the decrease in serum phosphate that occurred with mild HV alone (P = 0.33) (Table 1). Serum glucose rose from a baseline level of 4.93 ± 0.34 mmol/l to 11.81 ± 0.94 mmol/l at the end of the infusion, and then fell to 7.77 ± 0.75 mmol/l at 50 min after the end of the infusion.

**DISCUSSION**

In this study we have accurately graded HV and have recorded unique data on the changes in serum phosphate levels during and particularly after a period of HV. We have demonstrated significant falls in serum phosphate induced by mild and severe HV. Moreover, we have shown that the serum phosphate level continued to fall after the cessation of HV, a phenomenon that occurred in each of our HV protocols. This has not been shown before. We also demonstrated a significant fall in serum phosphate induced by dextrose infusion. When combined with mild HV, this appeared to have an additive hypophosphataemic effect.

The phenomenon of HV-induced hypophosphataemia has been well described [3,4,6,9,12]. Few studies have recorded detailed data on the post-hyperventilatory changes of serum phosphate, and none have shown a continuation of the fall in serum phosphate after cessation of HV. Staubli et al. [12] demonstrated a significant fall in serum phosphate with 20 min of unquantified HV. In...
their study, serum phosphate was measured at baseline, during the period of HV and at 75 min after cessation of HV. Serum phosphate fell significantly during the period of HV. When next measured, after 75 min of recovery, serum phosphate remained significantly low, but was returning to normal. We feel that our study methodology has a particular strength in the examination of the time course of the post-HV changes in serum phosphate. The other unique feature of our study is the continuous objective assessment of the degree of HV. Recent studies of HV have relied on devices to determine the respiratory rate [2,3,12] without a continuous objective measure of HV-associated hypocapnia. No other groups have used \( \text{PETCO}_2 \) as a record of degree of HV.

A number of possible mechanisms may explain the effect of HV on serum phosphate levels. Potential explanations include alterations in acid–base status [4,9] and glucose metabolism [4,9]. Sympathetic activity [20] may also affect serum phosphate, although this is an unlikely cause of HV-induced hypophosphataemia, as respiratory alkalosis has been associated with a decrease in sympathetic activity in a number of studies [21–23].

In our study the prolonged and continued decline in serum phosphate post-HV may have been related to alkalosis. Interestingly, however, alkalosis was resolving while serum phosphate continued to fall. For both mild and severe HV, pH values were virtually normal at the time of the maximum fall in serum phosphate. As has been speculated previously, an alternative explanation for the prolonged and progressive hypophosphataemia may relate to a prolonged period of intracellular alkalosis [4] after HV that is not reflected by serum pH values.

Changes in serum glucose may affect serum phosphate [9]. Although less marked than the rises that occurred with the dextrose infusion, serum glucose showed a significant overall elevation with both degrees of HV. It is possible that the mild hyperglycaemia associated with HV contributed to HV-induced hypophosphataemia.

Other consequences of HV that have been discounted as a cause of the fall in serum phosphate include renal excretion, precipitation as a salt and conversion into red cell organic phosphates [4]. With regard to the last point, an acute fall in erythrocyte ATP levels subsequent to HV has been demonstrated [12]. This fall in ATP levels followed the changes in serum pH more closely than the changes in serum phosphate, and the authors concluded that alkalosis was probably the more critical factor.

We assessed the effects of HV on other biochemical parameters. Mild HV was associated with a fall in serum potassium and a rise in serum glucose. The other parameters did not change significantly. Severe HV was associated with significant changes in serum potassium (which fell), total calcium (which rose) and serum magnesium (which fell). Otherwise the observations were similar to those made for mild HV. Although previous HV studies have shown variable changes in potassium [3,4], our study clearly showed a significant fall in potassium in both mild and severe HV. This can be explained by alterations in pH. In contrast with our study, Hafen et al. [3] noted no change in total magnesium, although they did find a significant fall in ionized magnesium, which we did not measure.

We measured an elevation in total serum calcium with severe HV. There was no change in total serum calcium with mild HV alone or with intravenous dextrose alone. Total serum calcium fell with mild HV plus intravenous dextrose infusion until 50 min after HV ceased, after which it rose. An increase in serum pH has been associated with a fall in total calcium [24]. Although we did not reproduce these findings, possible mechanisms include a decrease in protein binding of calcium with alkalosis [6,24] and alkalosis-induced bone calcium accretion [6].

We also recorded a significant post-hyperventilatory fall in oxygen saturation. This was more marked with severe HV than with mild HV. This has been noted previously [1], and postulated mechanisms include hyperventilation and an alteration of the hypoxic ventilatory response [1].

Our findings may have significant clinical implications. Patients with significant hypoxaemia due to a variety of cardiorespiratory diseases (including acute severe asthma, pneumonia, pulmonary thromboembolism and pulmonary oedema) may hyperventilate and develop hypophosphataemic respiratory alkalosis. Respiratory muscle weakness has been demonstrated in hypophosphataemic patients [7,8], with an improvement in muscle strength once serum phosphate is restored to normal. As the duration of hyperventilation in such subjects is likely to be very much longer than in the present study, hypophosphataemia may be prolonged for many hours after therapy and resolution of the underlying disorder. This persistent hypophosphataemia may, in turn, have significant cardiorespiratory effects. From the respiratory viewpoint, diaphragmatic weakness is likely, and this will impair alveolar ventilation in spontaneously breathing patients while potentially causing difficulty with weaning from mechanical ventilation [8]. Although changes in 2,3-DPG were not observed in our study, this is certainly conceivable with more prolonged hypophosphataemia, with resultant effects on the oxygen dissociation curve [10]. Hypophosphataemia has also been shown to cause myocardial dysfunction [25], with significant improvement in left ventricular systolic function after phosphate repletion. This may be particularly relevant to hyperventilating patients with haemodynamically significant pulmonary embolism or cardiogenic pulmonary oedema. In intensive care settings, patients requiring mechanical ventilatory support may undergo periods of HV as part of ventilatory management, e.g. patients with head trauma [26]. Patients with primary hyperventilation syndromes (anxiety, hys-
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Received 13 May 1999/3 December 1999; accepted 18 February 2000

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In summary, we have measured in detail the effects of increasing degrees of HV on serum phosphate levels. We have also demonstrated that the hyperventilatory fall in phosphate is sustained well beyond the completion of the hyperventilatory episode. Our results show that the decrease in phosphate levels during HV is potentiated by glucose loading. The clinical implications of these findings, particularly in the intensive care setting, warrant further study.

ACKNOWLEDGMENTS

We gratefully acknowledge the invaluable assistance of Patricia Beal (Department of Haematology, New Children’s Hospital, Sydney, NSW, Australia), Tony Whitton (Department of Biochemistry, Manly Hospital, Sydney, NSW, Australia) and Petra Macaskill (Department of Public Health and Community Medicine, University of Sydney, NSW, Australia) in the preparation of this manuscript.

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