Pharmacologic Elevation of Blood Inorganic Phosphate in Hypoxemic Patients with COPD*

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We have shown that in patients with COPD, myocardial efficiency during exercise is enhanced following acute elevations of plasma phosphate (Pi). A decrease in Hb-O2 affinity (increase in P50) was not responsible for the improvement. We postulated that the physiologic benefit was due to the acute reversal of a subclinical myocardial Pi depletion. To further test this hypothesis in a chronic state, we studied nine stable hypoxemic (PaO2 = 64 ± 2 mm Hg [± SEM]) patients with COPD over five weeks: two weeks at normal plasma Pi; and three weeks at elevated plasma Pi, induced by etidronate disodium (Didronel; 750 mg orally daily). Administration of etidronate disodium increased (p < 0.05) plasma level of Pi (4.4 ± 0.2 to 5.8 ± 0.1 mg/dl), RBC level of Pi (3.1 ± 0.2 to 4.1 ± 0.2 mg/dl), RBC level of 2,3-DPG (16.2 ± 1.1 to 21.3 g ± 1.3 μmol/g of Hb) and P50 (23.7 ± 0.5 to 26.0 ± 0.8 mm Hg). At the end of the treatment, the widening of the (a-v)O2 curve with exercise (7.1 ± 0.5 to 8.9 ± 0.6 ml/dl) was less pronounced than under control conditions (6.9 ± 0.4 to 10.1 ± 0.6 ml/dl; p < 0.02); concomitantly, the crossover point (COP; the PaO2 below which a rightward-shifted Hb-O2 curve causes the (a-v)O2 to become narrower rather than wider) increased (37 ± 2 to 49 ± 1 mm Hg). Indicators of myocardial work efficiency were not affected by etidronate disodium at rest or during exercise. We postulate that during exercise the potential beneficial effect of the rightward shift of the Hb-O2 curve upon cardiac function was negated by the fall of PaO2 to or below the COP level, a situation which would limit increases in tissue O2 extraction. (Chest 1991; 100:147-50)

W e have shown that normal subjects exercise more efficiently with acute plus chronic elevations of blood Pi, presumably due to a decrease in Hb-O2 affinity and thus enhanced tissue O2 extraction. We have also shown that patients with stable, hypoxemic COPD can exercise more efficiently when their blood Pi was raised acutely. In contrast to normal subjects, this effect could not be attributed to changes in Hb-O2 affinity; thus, we postulated that elevated Pi increased the efficiency of myocardial or skeletal muscle (or both), an effect opposite that described with hypophosphatemia. The present study was designed to determine if, in patients with COPD, the beneficial effects on exercise performance previously seen with acute elevations of blood phosphate persist when hyperphosphatemia is maintained on a chronic basis.

MATERIALS AND METHODS

The experimental protocol was approved prior to the study's initiation by the Committee for Protection of Human Subjects, University of Rome, and proceeded according to the Declaration of Helsinki. Nine stable ambulatory patients (eight men; one woman) were investigated. All demonstrated advanced COPD on the basis of clinical findings and physiologic tests. Pertinent characteristics included the following (mean ± SEM): age, 65 ± 3 years; body surface area, 1.78 ± 0.4 m²; FEV1, 1.0 ± 0.1 L; FVC, 2.2 ± 0.1 L; arterial pH on room air, 7.37 ± 0.02; PaO2, 64 ± 2 mm Hg; and PaCO2, 45 ± 2 mm Hg.

The experimental design is depicted in Figure 1. Each study lasted five weeks. After a control period of two weeks, etidronate disodium (Didronel; 750 mg orally daily) was given for three weeks; the sequence of control and etidronate disodium was randomized. On day 1 at 8 AM, venous blood was drawn for measurement of plasma and RBC levels of Pi (Sigma Kit No. 360-UV) and Hb-O2 affinity (PaO2; the PaO2 required to half saturate Hb) along with the following major factors capable of affecting the position of the Hb-O2 curve: RBC pH by freeze-thaw method; 2,3-DPG (Sigma Kit No. 35-UV); MCHC (from Hb and Hct); and CoHb and MetHb (CO-Oximeter IL 282). Shortly thereafter, the following physiologic parameters were determined: mean BP by automatic sphygmomanometry (Dinamap; Critikon Inc); Ve and VO2 (Oxylog, EK Morgan Ltd); cardiac output, SV, HR, and SEF by impedance cardiography (Minnesota Impedance Cardiograph 304B) and microcomputer (Surcom Inc); and (a-v)O2 calculated from VO2 and cardiac output. For the basal and the experimental conditions, the COP (the PaO2 at which there is no difference in mixed-venous PO2 between the standard curve and the shifted curve at constant O2 uptake) was calculated by standard methods. A five-minute submaximal ergocycle exercise was then performed at a work rate of 25 ± 1 W, approximately 60 percent of the patients' VO2 peak (which was established one week prior to initiation of the study). During the fifth...
EXERCISE
CARDIORESPIRATORY VARIABLES

Figure 1. Experimental design. On day 1, P<sub>50</sub> was measured, and exercise testing was performed; O<sub>2</sub> transport parameters were measured just before and during last minute of exercise. Same sequence was repeated at end of treatment with etidronate disodium (Didronel) on day 35.

minute of exercise, the physiologic determinations listed previously were repeated. The entire sequence was repeated at the end of the third week of treatment, at the same work rate of 25±1 W.

Statistical methods utilized paired t-tests and Pearson product-moment correlation analysis with the level of significance set at p<0.05.

RESULTS

The administration of etidronate disodium induced elevations of the plasma level of Pi, the RBC level of Pi, the RBC level of DPG, and in vivo P<sub>50</sub> (Table 1).

![Image of data table]

Table 1—Physiologic Parameters during Control and Treated Periods*  

<table>
<thead>
<tr>
<th>Data</th>
<th>Control Rest</th>
<th>Control Exercise</th>
<th>Treatment Rest</th>
<th>Treatment Exercise</th>
</tr>
</thead>
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<tr>
<td>RBC pH</td>
<td>7.13±0.01</td>
<td>7.12±0.01</td>
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<tr>
<td>MCHC, %</td>
<td>32±0</td>
<td>31±0</td>
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<td>CoHb + MetHb, %</td>
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<td>2.2±0.2</td>
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<tr>
<td>2,3-DPG, μmol/g Hb</td>
<td>16.2±1.1</td>
<td>21.3±1.3†</td>
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<tr>
<td>Pa&lt;sub&gt;m&lt;/sub&gt;, mm Hg</td>
<td>23.7±0.5</td>
<td>26.0±0.8†</td>
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</tr>
<tr>
<td>Plasma Pi, mg/dl</td>
<td>4.4±0.1</td>
<td>5.8±0.1†</td>
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<tr>
<td>RBC Pi, mg/dl</td>
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<td>4.1±0.2†</td>
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<td>SV, ml</td>
<td>54±5</td>
<td>57±7</td>
<td>87±6</td>
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<td>Cardiac output, L/min</td>
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<td>3.9±0.3</td>
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<td>SEF, percent</td>
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<td>57±3</td>
<td>60±3</td>
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<tr>
<td>HR, beats per min</td>
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<tr>
<td>V&lt;sub&gt;Es&lt;/sub&gt;, L/min</td>
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<td>277±14</td>
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<td>C(a-v)&lt;sub&gt;O&lt;/sub&gt;&lt;sub&gt;2&lt;/sub&gt;, ml/dl</td>
<td>6.9±0.4</td>
<td>7.1±0.8</td>
<td>8.9±0.6</td>
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*Table values are means ± SEM.
†p<0.05 vs control.

Figure 2. Effect of rightward shift of Hb-O<sub>2</sub> curve upon C(a-v)<sub>O</sub><sub>2</sub> at various Pa<sub>O</sub><sub>2</sub> levels. A (left): Pa<sub>O</sub><sub>2</sub> is higher than COP. With increased F<sub>ao</sub>, reduction in Ca<sub>O</sub><sub>2</sub> (O<sub>2</sub> loading in lungs) is smaller than reduction in Cv<sub>O</sub><sub>2</sub> (O<sub>2</sub> unloading in tissues), and the C(a-v)<sub>O</sub><sub>2</sub> widens (x>y). B (center): Pa<sub>O</sub><sub>2</sub> is lowered to equal COP. With increased F<sub>ao</sub>, reduction in Ca<sub>O</sub><sub>2</sub> is same as reduction in Cv<sub>O</sub><sub>2</sub>, and C(a-v)<sub>O</sub><sub>2</sub> remains unchanged (x=y). C (right): Pa<sub>O</sub><sub>2</sub> lowered below COP level. With increased F<sub>ao</sub>, reduction in Ca<sub>O</sub><sub>2</sub> is larger than reduction in Cv<sub>O</sub><sub>2</sub>, and C(a-v)<sub>O</sub><sub>2</sub> narrows (x<y).
There was a significant relationship ($r=0.66; p<0.05$) between elevations of DPG and elevations of $P_{50}$. The RBC pH, MCHC, CoHB level, and MetHb level remained unchanged (Table 1). Under control conditions, COP was $35 \pm 2$ mm Hg at rest and $49 \pm 1$ mm Hg during exercise; under experimental conditions (etidronate disodium), COP was $37 \pm 2$ mm Hg at rest and $49 \pm 1$ mm Hg during exercise.

During the control period at rest, all measured physiologic parameters were within the normal range (Table 1), as reported previously. During each exercise bout the duration and the work rate were identical, and the responses of HR, BP, $V_E$, and $V_O_2$ were consistently the same (Table 1). The $C(a-v)O_2$ widened during exercise; at the end of the experimental phase, this widening was statistically less pronounced than under control conditions ($1.8 \pm 0.7$ vs $3.3 \pm 0.5$ ml/dl; $p<0.02$). On the experimental day, all other resting and exercise values were similar to the corresponding values during the control period.

**DISCUSSION**

The chronic administration of etidronate disodium resulted in the anticipated sustained elevation of blood inorganic and organic phosphate compounds and, consequently, a proportional rightward shift of the Hb-O$_2$ dissociation curve. A rightward-shifted Hb-O$_2$ curve should yield a wider $C(a-v)O_2$ difference, lower cardiac output, and equal $V_O_2$. However, in our study the $C(a-v)O_2$ was smaller than during the control period, a seemingly paradoxical response to equal $O_2$ demands. The most likely explanation relates to the influence of the COP (the PaO$_2$ at which the $C[a-v]O_2$ difference becomes narrower rather than wider, with a rightward-shifted curve). This postulate is illustrated diagrammatically in Figure 2. Factors known to influence the COP are the hemoglobin concentration, the $C(a-v)O_2$, and the $P_{50}$. In the control state the COP at rest was $35 \pm 2$ mm Hg. During exercise the $C(a-v)O_2$ rose to $10.1 \pm 0.6$ ml/dl, and the COP increased to $49$ mm Hg, but presumably remained below the level reached by the falling PaO$_2$. In the experimental state the resting COP was higher ($37 \pm 2$ mm Hg) than the control state due to the rightward shift of the Hb-O$_2$ curve. If the exercise values for $C(a-v)O_2$ had widened as much as in the control state, the COP would have risen to approximately 54 mm Hg and thus likely become higher than the exercise PaO$_2$. It seems reasonable that under those conditions $C(a-v)O_2$ would rise less, preventing the COP from exceeding the PaO$_2$. This was indeed the case, as the change in $C(a-v)O_2$ during exercise with etidronate disodium remained lower than control, keeping the COP at 49 mm Hg.

In patients with COPD, the response of PaO$_2$ to exercise is quite variable and is dependent primarily upon the resting level of PaO$_2$ and the type of physical effort demanded of the subjects. In studies utilizing patients and exercise conditions comparable to ours, PaO$_2$ fell on average by as much as 14 mm Hg.

Other explanations for the observed findings are less attractive; they include the possibility that the overall results, control vs etidronate disodium, are not different and that greater increases in $P_{50}$ are required before any beneficial effect can be observed. Perhaps phosphate homeostasis was different between subjects in the present study vs the previous one. This is unlikely, since plasma phosphate levels between the two studies were similar. There is also the possibility that etidronate disodium, per se, contributed to our results via some unexplained mechanism. The present data are most compatible with the hypothesis that the beneficial effect at the tissue level of a rightward shift in the Hb-O$_2$ curve ceases to be operative when the PaO$_2$ approaches the COP.

These negative results should not prevent similar trials in clinical states characterized by reasonably normal PaO$_2$, such as patients with coronary artery disease or anemia, where heightened tissue oxygen demands may be improved by chronic elevation of blood Pi. As for patients with COPD, more comprehensive investigations, to include additional O$_2$ transfer parameters and phosphate balance data, with a precise accounting of intramuscular phosphate compounds by nuclear magnetic resonance spectroscopy, are needed to clearly define the potential efficacy of various forms of induced hyperphosphatemia as an ergogenic aid.

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