Oxyhemoglobin Affinity in Bronchial Asthma: Chronic Stable State, Acute, and Status Asthmaticus*

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Studies in chronic stable bronchial asthma revealed normal $P_{50}$; COLD controls exhibited significantly elevated $P_{50}$ and 2,3-DPG levels. In patients with acute asthma, no differences in $P_{50}$ or 2,3-DPG were discernible. Subdivision of acute asthma into categories with hyperperventilation ($PaCO_2 \leq 37.0$ mm Hg) and hyperventilation ($PaCO_2 > 37.1$ mm Hg) revealed that hyperventilating patients exhibited a mean $P_{50}$ of $27.7 \pm 4.3$ mm Hg unchanged over normal controls or chronic stable asthma while hyperventilating subjects were significantly left-shifted ($P_{50} = 25.1 \pm 0.7$ mm Hg) contrasted with normal and stable asthmatic patients ($P < 0.001$) despite significant oxyhemoglobin desaturation (80.2 percent). 2,3-DPG data paralleled these observations. The pH was found to influence the $P_{50}$ change in the hyperventilating population. MCHC measurements, percent HbCO or hemoglobin was not related. While the Bohr effect, reflected in estimates of physiologic in vivo $P_{50}$ values, tends to temper leftward shifts in asthma associated with respiratory acidosis, the lack of compensatory increase in 2,3-DPG and an associated elevated $P_{50}$ in spite of the hypoxic stimulus, may limit maximal oxygen delivery to tissues.

**MATERIALS AND METHODS**

**Patient Selection**

Twenty-eight patients with bronchial asthma were selected on the basis of a clinical history of continuous or episodic wheezing and dyspnea, allergic diathesis, airways obstructive disease pattern with at least a 15 percent response in FVC or $FEV_1$ percent following aerosol isoproterenol therapy, dermal reactivity to standard allergens, blood and sputum eosinophilia, and the absence of chronic bronchitis or pulmonary emphysema by clinical, radiologic and physiologic features. Patients with acute or chronic, stable asthma were defined by the clinical history, spirometry and blood gas changes; the acute or status asthmaticus state was also qualitatively graded as to severity by a 1 to 4+ (4+ = status asthmaticus) score by these same factors. In some cases more than one acute study was conducted in a given patient but this was always a different episode (Table 1). No patient had a history of congestive heart failure, anemia, thyrotoxicosis, alcoholism or known hemoglobinopathy and no attempt was made to control cigarette consumption. Medications were not altered during the study, and as a group the following were being employed: aminophylline preparations, aerosol isoproterenol, glyceryl guiacolate, adrenal corticosteroids, a combination of theophylline, ephedrine and phenobarbital (Tedral), various antihistamine preparations and antimicrobials.

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Two groups of subjects served as controls (Table 1). In the
first instance 17 normal volunteers without any complicating
disorders known to influence oxyhemoglobin affinity were
selected. A second type of control consisted of 12 patients
with chronic obstructive lung disease (COLD) and signif-
cant arterial hypoxemia who were studied during the same
period as the asthmatic population.

All blood sampling was performed prior to spirometric
studies or oxygen administration. Where possible, the stable
to acute phase asthmatic observations were performed in a
paired fashion; that is the chronic stable patient serving as
the control for the acute asthmatic attack study.

Methods
Oxygen-hemoglobin affinity was quantitated by the P02, the
partial pressure of O2 in mm Hg corresponding to 50 percent
of oxyhemoglobin saturation at pH 7.40 and 37°C. An increased
Po2 reflects a decrease in the affinity of hemoglobin for
oxygen, or a rightward shift of the oxyhemoglobin dissoci-
ation curve. Fresh, heparinized arterial blood drawn anaero-
obically at rest (after three to five minutes to minimize
P02 checks of the zero point were conducted by addition of
carbon monoxide.° Hill's constant "n" was obtained from the
slope of the plot log Y against log P02 employing the formu-
lation of P02 » 100 (Hb02) (1 + Hb02 / Hb02 + HbCO). The
three corrected P02 values corresponding to 50 percent, 30
percent, and 50 percent oxygen, each containing 5.6 percent
carbon dioxide and the balance nitrogen, at 6 L/min were
agitated at 37°C with humidi\ed gas mixtures of 1.5 percent,
3.0 percent, and 5.0 percent oxygen, each containing 5.6 percent
carbon dioxide and the balance nitrogen, at 6 L/min flow.
This yielded approximate in vitro tensions of 11, 21 and 36
mm Hg respectively for oxygen and 40 mm Hg for CO2.

A three wavelength spectrophotometric system (IL-182-
CO-oximeter, Instrumentation Laboratory) was employed for
analysis of total hemoglobin, oxyhemoglobin (Hb02) and
carboxyhemoglobin (HbCO). The spectrophotometer matrix
is calibrated from blood samples of known hemoglobin satu-
ration by methods previously described.°7 Frequent daily
checks of the zero point were conducted by addition of
freshly prepared sodium dithionite to 2 ml of arterial blood,
and of the 100 percent point by 100 percent oxygen in equi-
ibrated blood, accounting for percentage HbCO.

Following 15 minutes' equilibration in the tonometer, in-
ccluding syringe mixing each five minutes, assays were con-
ducted for oxygen saturation and carboxyhemoglobin concen-
tration in the CO-oximeter and for P02, Pco2 and pH in the
Instrumentation Laboratories blood gas analyses model
no. 313 at 37°C. Duplicate or triplicate readings generally
agreeing within 0.5 percent for oxygen saturation and carbon
monoxide concentration, and 0.5 to 1.0 mm for P02 and
Pco2 and within 0.05 to 0.01 for pH were performed for each
sample and the results averaged. The P02 was corrected for
the Bohr effect (plasma pH variation) to pH of 7.40 by
employing the Severinghaus nomogram.° The Pco2, HbCO, was
then determined graphically from a log-log cycle plot of the
three corrected P02-oxyhemoglobin saturation points em-
ploying the y axis for 100-percent saturation and corrected
P02 directly on the abscissa. The best line, visually estimated
through the three points, served as the basis for the graphic
solution of P02,co2. In the presence of widely divergent
pH points the entire study was repeated. The P02 at pH 7.40
value was finally corrected for the Haldane-Smith effect in all
patients who smoked cigarettes, due to the presence of
carboxyhemoglobin, employing the formulation of Roughton
and Darling: P02 corrected = P02 original 1 + HbCO / Hb02
the corrected P02 corresponding to a saturation value equal
to the sum of the hemoglobin saturation with oxygen and
carbon monoxide.° Hill's constant "n" was obtained from the
slope of the plot log Y against log P02 where Y equals
the fraction of oxyhemoglobin. A decrease in "n" indicates a
tendency for less heme-heme interaction. Physiologic, in vitro

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Table 2—Comparison of Controls and Patient Population: Selected Parameters.

<table>
<thead>
<tr>
<th>Group: Parameter</th>
<th>Stable Asthma * vs Stable Asthma †</th>
<th>Stable Asthma * vs Normals</th>
<th>Acute Asthma * vs Normals</th>
<th>Normals vs COLD †</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P50 (corrected CO)</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>PaO2, mm Hg</strong></td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>SaO2, %</strong></td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>PaCO2, mm Hg</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>HCO3−, mEq/L</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>Hgb, gm %</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>2,3-DPG, µM/1010 RBC</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>ATP, µM/1010 RBC</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>HbCO, %</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>FVC, % predicted</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>FEV1.0%, % predicted</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td><strong>MCHC</strong></td>
<td>NS</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
<td>S, p &lt; 0.001</td>
</tr>
</tbody>
</table>

NS = Non-significant difference
S = Significant difference, p given
† = COLD
* = All acute asthmatics combined
† = Not shown P50 (corrected) COLD vs acute and stable asthma: Significant difference p < 0.001

P50, accounting for the Bohr effect, was determined by converting the final mean P50 value by the relationship: \( A \log P50/ApH = -0.48 \), where ApH is based on the actual plasma pH.\(^{10}\)

Oxygen and carbon dioxide electrode calibrations were made directly against humidified commercial gas mixtures having concentrations of about 5.3 percent CO2 and up to 12.0 percent O2, balance nitrogen were within the expected range of the study and which agreed to 0.06 percent as measured by the Scholander, microanalytic technique. All calibrated samples for Poe and Pco2 agreed within ± 1.0 mm Hg, and 0.005 units for pH and all standard calibrations were performed immediately before each sample was assayed.

Hemoglobin was determined spectrophotometrically; red blood cell counts were performed in the Coulter Counter, model B, and are expressed as number of RBC \( \times 10^6 \) per cu mm; microhematocrit was determined after five minutes and mean corpuscular hemoglobin concentration (MCHC) is expressed as gm Hb/100 ml red cells; simple pulmonary mechanics were obtained from a standard spirometer (BTPS).

A determination of 2,3-diphosphoglycerate was made by a modification of the method of Krimsky.\(^{11}\) A neutralized trichloroacetic acid extract was diluted in distilled H2O, and 0.06 ml was added to a 3.01 ml volume containing tris buffer (pH 7.4) 0.04 M, MgCl2 0.01M, phosphoenolpyruvate 0.025M, enolase (commercial muscle preparation) 0.05 mg, phosphoglycerate mutase (commercial muscle preparation) 0.05 mg.\(^*\) Change in O.D. was measured on the Beckman DU. A standard curve was made and the results expressed in µM/1010 red cells.

Adenosine triphosphate (ATP) was measured with the reagents of Sigma kit no. 366 according to directions in the technical bulletin. Results were calculated using the extinction coefficient for DPNH and are expressed as µM/1010 red cells.

**RESULTS**

**Clinical-Physiologic Parameters**

The mean (± 1 SD) values of pertinent clinical and physiologic data presented in Tables 1 and 2 indicate the nature of the asthmatic population. Chronic stable bronchial asthma was characterized by mild hypoxemia, hyperventilation and respiratory alkalosis. These patients were older than normal controls, but hemoglobin and HbCO levels were similar. In the acute attack (2.9 ± 0.9 + severity) greater hypoxemia and oxyhemoglobin desaturation (nomogram) developed. The mean pH of 7.39 ± 0.07 in the acute attack was significantly different from the pH of 7.44 ± 0.03 in the stable state (P<0.001). PaCO2 averaged the same for acute asthma and normal subjects. Neither age, hemoglobin nor percent HbCO were different among stable state versus acute asthmatics. The duration of the acute attack was 43.2 ± 24.3 hours. Analysis of paired observations, that is, a stable state serving as the control for an acute attack in the same patient, revealed a significant fall in PaO2 and SaO2 (P<0.001), HCO3− (P<0.05) and hemoglobin concentration (P<0.05); PaCO2, pH and HbCO were not significantly different.

The COLD patients, included as controls during the study period, exhibited similar degrees of arterial hypoxemia (PaO2 = 48.9 ± 10.9 mm Hg).

**P50 (corrected for CO) and Hill's Constant (n)**

The mean P50 7.40 in 26 stable asthmatics of 27.6 ± 1.6 mm Hg was not significantly different from normal subjects, 26.8 ± 0.3 mm Hg, or acute asthmatics, 26.4 ± 3.1 mm Hg. Similarly, the mean P50 7.40 in acute asthma was not different from normal or stable asthma. Additionally, paired data analysis revealed no difference in P50 7.40 in the acute attack compared with the chronic stable state.
Erythrocytic Organic Phosphate Changes

The mean (± 1 SD) concentration of erythrocytic 2,3-DPG in the normal controls of 3.44 ± 0.79 µM/10⁶ RBC was not significantly different from chronic stable or acute bronchial asthma with respective levels of 3.82 ± 1.32 and 3.17 ± 1.28 µM/10⁶ RBC. Similarly, acute and stable asthmatics as a group exhibited no differences in 2,3-DPG values (Tables 1 and 2). Paired data analysis (Table 3) correspondingly revealed similar 2,3-DPG levels in acute asthma compared with the same patient in the stable state. Data for ATP paralleled these 2,3-DPG observations. Patients with COLD manifested significant increases in 2,3-DPG compared with normal controls (P < 0.05) and acute asthmatics (P = 0.05).

Correlation analysis of all asthmatics as a group revealed no relationship between Pao7.40 and 2,3-DPG. There was a low (r = 0.32) relationship only between 2,3-DPG and arterial pH (P < 0.02). When the asthmatic population was divided into either stable or acute groups, no correlation between 2,3-DPG and Pao7.40, pH or other variables was observed.

Subdivision of Acute Bronchial Asthma into Hyperventilation and Hypocentilation Groups: Reanalysis of Parameters

Based upon a spectrum of ventilatory changes, the acute asthmatic patients were arbitrarily divided into two groups defined by their effective alveolar ventilation as indexed by PaCO₂: Hyperventilation when PaCO₂ ≤ 37.0 mm Hg, and hypocentilation (and cross-over phase) when PaCO₂ > 37.1 mm Hg.

Table 4—Subdivision of Acute Bronchial Asthma by Effective Alveolar Ventilation (PaCO₂): Comparison of Parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hyperventilation PaCO₂ &lt; 37.0 mm Hg</th>
<th>Hyperventilation PaCO₂ &gt; 37.1 mm Hg</th>
<th>Observations No.</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>35.3 ± 15.0</td>
<td>44.2 ± 15.4</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂ mm Hg</td>
<td>59.6 ± 9.9</td>
<td>48.9 ± 8.0</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂ %</td>
<td>89.5 ± 6.9</td>
<td>80.2 ± 8.1</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>31.2 ± 6.4</td>
<td>43.8 ± 5.4</td>
<td>15</td>
<td>S, p &lt; 0.02</td>
</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.07</td>
<td>7.35 ± 0.04</td>
<td>15</td>
<td>S, p &lt; 0.02</td>
</tr>
<tr>
<td>HCO₃⁻, meq/L</td>
<td>20.1 ± 3.8</td>
<td>23.3 ± 1.9</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Hgb, gm %</td>
<td>15.1 ± 1.9</td>
<td>14.7 ± 1.7</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>2,3-DPG, µM/10⁶ RBC</td>
<td>3.60 ± 1.80</td>
<td>2.76 ± 0.58</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>ATP, µM/10⁶ RBC</td>
<td>0.92 ± 0.64</td>
<td>0.92 ± 0.64</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Pao7.40, corrected CO</td>
<td>27.7 ± 4.3</td>
<td>25.1 ± 0.7</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Pao7.40, uncorrected CO</td>
<td>27.0 ± 3.9</td>
<td>24.9 ± 0.7</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>Duration, hr</td>
<td>41.1 ± 22.8</td>
<td>36.6 ± 20.5</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>HBCO₂, %</td>
<td>2.7 ± 2.2</td>
<td>0.70 ± 0.02</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>45.0 ± 10.4</td>
<td>38.5 ± 19.1</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Severity, 1-4+*</td>
<td>2.7 ± 0.8</td>
<td>3.4 ± 0.9</td>
<td>15</td>
<td>NS</td>
</tr>
<tr>
<td>MCHC</td>
<td>33.20 ± 6.0</td>
<td>30.52 ± 0.0</td>
<td>8</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = Non-significant  S = Significant difference, p given  * = 4+ most severe

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There were seven patients in the hyperventilation category and six with hypoventilation. Their mean ages, clinical severity, FVC (percent predicted), hemoglobin concentrations, percent HbCO and duration of symptoms were not statistically significantly different. PaO₂ tended to be lower in the hypoventilating group, but was not of statistical significance; SaO₂, however, was significantly lower. Mean PaCO₂ was higher (P<0.01) but this was due to arbitrary selection of cases. Corresponding pH was significantly more acid (7.35 ± 0.04) in the hyperventilating than the hypoventilating group (pH = 7.43 ± 0.07) (P<0.01). No differences in PaO₂, 2,3-DPG or ATP were found when these two groups were compared with each other (Table 4).

However, when the hyperventilating and hypoventilating groups were compared to chronic stable bronchial asthma or normal controls, differences were noted (Table 5). In the group with alveolar hypoventilation, the mean PaO₂ (corrected CO) of 25.1 ± 0.7 mm Hg was significantly lower than in chronic bronchial asthma, PaO₂ = 27.6 ± 1.6 mm Hg (P<0.001), and normal controls, PaO₂ = 26.8 ± 0.3 mm Hg (P<0.001). Similarly, the 2,3-DPG concentration (2.76 ± 0.58 µM/10¹¹ RBC) was significantly reduced over chronic stable asthma and normal controls (P<0.02 and P<0.02). ATP changes were not significant. Finally, the arterial pH of 7.35 ± 0.04 was more acid than stable asthma (P<0.001) and normal controls (P<0.001). PaCO₂ was significantly higher than in normal controls and in chronic stable asthma; HCO₃⁻ and hemoglobin were not significantly different.

Similar analysis for the subgroup of hyperventilating asthmatic subjects revealed no changes in PaO₂ (corrected CO) or 2,3-DPG; while PaCO₂ was lower (by selection), pH and HCO₃⁻ were not different from control normals or stable asthmatics. Other variables are presented in Table 5. Due to sample size limitations, correlation analyses were not performed in these subgroups.

Finally, the total group of asthmatic patients was arbitrarily divided into two groups according to PaO₂ (<55 and >55 mm Hg); no differences in PaO₂, 2,3-DPG or other variables were noted.

MCHC measurements were not statistically different between control subjects and patient groups (Table 1).

**DISCUSSION**

In the present study oxygen-hemoglobin affinity was examined in a group of asthmatic patients

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**Table 5—Comparison of Acute Asthma Versus Normal Controls and Stable Bronchial Asthma.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PaCO₂ &lt; 37.0 mm Hg</th>
<th>PaCO₂ &gt; 37.1 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
<td>N*</td>
<td>Acute Vs Stable Asthma</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>32</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td>Hb, %</td>
<td>32</td>
<td>S, p &lt; 0.02</td>
</tr>
<tr>
<td>HbCO, %</td>
<td>32</td>
<td>S, p &lt; 0.02</td>
</tr>
<tr>
<td>ATP, µM/10¹⁰ RBC</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>36</td>
<td>NS</td>
</tr>
<tr>
<td>MCHC, %</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>HbCO, %</td>
<td>32</td>
<td>NS</td>
</tr>
<tr>
<td>PaO₂, uncorrected</td>
<td>34</td>
<td>NS</td>
</tr>
<tr>
<td>Parameter</td>
<td>PaCO₂ &gt; 37.1 mm Hg</td>
<td>N*</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>33</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>32</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td>Hb, %</td>
<td>32</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td>HbCO, %</td>
<td>32</td>
<td>S, p &lt; 0.001</td>
</tr>
<tr>
<td>ATP, µM/10¹⁰ RBC</td>
<td>33</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>MCHC, %</td>
<td>32</td>
<td>S, p &lt; 0.02</td>
</tr>
<tr>
<td>PaO₂, uncorrected</td>
<td>35</td>
<td>S, p &lt; 0.001</td>
</tr>
</tbody>
</table>

*Number of observations.*
exhibiting various degrees of hypoxemia and ventilatory competence. Under chronic stable state conditions of approximately 12 days’ duration, modest impairment of oxygen transfer in association with hypocapnia and respiratory alkalosis was present; however, SaO2 was normal. Under these circumstances neither shifts in oxyhemoglobin affinity by PaO2 nor changes in intraerythrocytic organophosphate were observed. Based upon reports in the literature, the levels of SaO2 and pH for this group with stable bronchial asthma are not of sufficient magnitude to alter 2,3-DPG biosynthesis or otherwise influence P50. The in vivo position of the oxygen-hemoglobin association-dissociation curve may, however, be somewhat left of normal in stable asthma due to a Bohr effect related to chronic respiratory alkalosis.

The pathophysiologic conditions of an acute bronchial asthmatic attack are, however, complex and despite the observation of a mean severity of 3+ (out of a possible 4+) score, one cannot predict the status of oxygen delivery to the tissues. Criteria other than PaCO2 and pH, such as FVC, PaO2, SaO2, age, etc, may be quite similar in hyperventilating or hypoventilating subjects with acute asthma. Therefore, to pool all such patients as a group might obscure significant changes in P50 related largely to carbon dioxide and to pH. Thus, in the present study, P50 measurements in acute bronchial asthmatic patients compared with normal controls and chronic stable bronchial asthma were statistically similar suggesting no hemoglobin adaptation despite significant hypoxemia and oxyhemoglobin desaturation. In addition mean PaCO2 and pH were normal and would exert no effect upon 2,3-DPG levels. This conclusion is based upon group data and supported by paired observations.

However, the clinical spectrum of an acute asthmatic attack encompasses not only variable degrees of progressive hypoxemia, but may also be separated into stages of appropriate alveolar hyperventilation and uncompensated alveolar hypoventilation. The latter may also include a “relative hyperventilation” with approximately normal PaCO2 and pH values, the so-called “cross-over point,” which, in the clinical context, reflects a deteriorating phase preceding frank hypercapnia and respiratory acidosis. Accordingly, a group of acute asthmatic patients may represent a heterogeneous population in terms of carbon dioxide clearance (effective alveolar ventilation) and the net effect upon arterial pH. This is reflected in the data of this series by the normal PaCO2 and pH of the grouped acute asthmatic subjects.

When patients with acute bronchial asthma were divided into those with alveolar hyperventilation or those with progressive or overt hypoventilation by both clinical and PaCO2 indices, certain interesting features were identified. In the group of hyperventilating patients, significant hypoxemia with a PaO2 of 59.6 ± 9.5 mm Hg was present in conjunction with hypocapnia and respiratory alkalosis. Despite the presence of these two factors, P50 remained unchanged; 2,3-DPG was similarly not increased in this group over normal controls or stable state asthmatics. The cause for this failure of response is unclear from our data in view of the reports of rightward P50 shifts under similar conditions in other diseases. Other than significant hypocapnia and hypobasemia, the other factors examined in this study, including changes in red cell volume (MCHC), appeared not to be distinctive in these clinically compensated hyperventilating acute asthmatic patients.

Those asthmatic patients with relative or frank hypoventilation were acidic with significantly lower SaO2 levels; nevertheless, they exhibited a significantly reduced P50 when compared to both chronic stable state asthma or normal control subjects (P<0.001). Correspondingly, erythrocytic 2,3-DPG levels were significantly reduced (P<0.02). Thus these patients not only failed to adapt their P50 but were left-shifted despite significant hypoxemia and oxyhemoglobin desaturation. This effect may be in part ascribed to the coexisting hypercapnia and respiratory acidosis. Similar pH related effects, paralleling this hypercapnic-respiratory acidic suppression in acute asthma have been described: altitude induced increases in 2,3-DPG are prevented by concurrent administration of acidifying agents; inspired carbon dioxide administered to hypoxic rats prevents increases in red cell 2,3-DPG; anemic or anoxic patients with acidosis have low 2,3-DPG concentrations. Thus these observations in acute and status asthma support the concept that the time average Hi-HbO2 ratio is not the total nor dominant regulatory mechanism for P50 shifts and that plasma and intraerythrocytic pH changes, and perhaps elevated carbon dioxide concentrations as well, exert, in a multifactorial interaction, significant control in oxygen-hemoglobin equilibria.

The only significant correlations observed in this study were between P50 and pH and between 2,3-DPG and pH. They are in agreement with the above cited effects of pH upon 2,3-DPG and P50. Based upon the observations that the formation of carboxyhemoglobin compounds, due to increases in Pco2, elevate P50 of constant pH hemoglobin solutions.
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Severe asthmatic conditions require conditions favoring tissue hypoxia than is evident from usual blood gas or clinical parameters, and until proved otherwise should be guarded against "dangerous" levels of hypoxemia. This problem appears to be further compounded by actual leftward shifts in $P_{50}$ that appear partially pH dependent in hyperventilating asthmatic patients; this may further limit oxygen delivery and add to the burden of cardiorespiratory work. These statements must, however, be qualified by the influence of the direct Bohr effect, which may offset pH related 2,3-DPG suppression and result in more physiologic in vivo oxygen-hemoglobin relationships. When the mean in vivo $P_{50}$ was determined for the group of hyperventilating asthmatic patients, a value for $P_{50}$ of 26.2 mm Hg was found indicating that a rightward shifting tendency was present, partially compensating for the acidosis in contrast to the $P_{50}$ determined at pH 7.40 of 25.1 mm Hg. Conversely, this argument may be applied to hyperventilating asthmatics who would, for example from the data of this study, shift leftwards from $P_{50} = 27.7$ mm Hg at pH 7.40 to $P_{50} = 26.8$ mm Hg at a pH of 7.43. However, the critical experiments of actual tissue delivery of oxygen are yet to be performed to further clarify these changes in oxygen releasing capacity in bronchial asthma within the context of cardiovascular, red cell mass and ventilatory mechanisms.

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