Effectiveness of Oxygen Therapy in Hypoxic Polycythemic Smokers*

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Eleven hypoxic (arterial oxygen pressure [PaO₂] ≤ 61 mm Hg), polycythemic (hematocrit reading ≥ 54 percent) patients were studied to determine the effect of the carboxyhemoglobin level on their response to therapy with supplemental oxygen. Five nonsmokers with a mean carboxyhemoglobin level of 2.8 percent showed an excellent response to therapy with supplemental oxygen, with a decrease in hematocrit reading from 57 percent to 57 percent (P < 0.0025) as the PaO₂ increased from 53 mm Hg to 69 mm Hg (P < 0.0025) and the SaO₂ increased from 82 percent to 88 percent (P < 0.01). In spite of similar values for the PaO₂, the smokers had higher hematocrit readings before and during therapy with oxygen (P < 0.01), presumably due to superimposed desaturation by carboxyhemoglobin. We concluded that polycythemia in hypoxic smokers is due to additive effects of hypoxia and a high carboxyhemoglobin level. The former is responsive to therapy with oxygen, while the latter is not. To achieve a “complete” response to therapy with supplemental oxygen, hypoxic polycythemic smokers should quit smoking.

Reversible secondary polycythemia due to chronic oxygen desaturation commonly occurs in patients with chronic hypoxia (decreased arterial oxygen pressure [PaO₂]). This condition has been described in patients living at high altitude, in those with cyanotic congenital heart disease, and in those with pulmonary disease and may be reversed by correction of the hypoxia. In persons dwelling at high altitude, the polycythemia may be reversed by moving to sea level. In cyanotic congenital heart disease, the polycythemia may be reversed by surgical correction of the lesion. Patients with polycythemia secondary to pulmonary disease may have reversal of the polycythemia with medical therapy, including administration of supplemental oxygen. This reversal does not occur in all patients with polycythemia secondary to hypoxic pulmonary disease, and it is unclear what separates those who respond to such therapy from those who do not.

More recently, reversible polycythemia has been described in some smokers with normal values for PaO₂, and the condition is believed to be caused by markedly elevated carboxyhemoglobin concentrations. Cessation of smoking resulted in reversal of the polycythemia as the carboxyhemoglobin levels returned to normal. It has been postulated that therapy with supplemental oxygen would not evoke a response in these patients, since the oxygen desaturation was not due to a low PaO₂ but to elevated concentrations of carboxyhemoglobin. In a recent study of people dwelling at high altitude, most patients with polycythemia were found to be cigarette smokers, which suggests that an increased carboxyhemoglobin level is an additive factor to hypoxia in causing polycythemia.

It is well known that patients with chronic pulmonary disease may continue to smoke and have elevated concentrations of carboxyhemoglobin. The secondary polycythemia that occurs in some of these patients may be a result of hypoxia or carboxyhemoglobinemia (or both). Studies of therapy with oxygen in patients with secondary polycythemia due to pulmonary disease have not included inquiry into smoking habits and measurements of carboxyhemoglobin levels. This information might be helpful in explaining the variable response to therapy with supplemental oxygen and in predicting who will respond. It is possible that elevated concentrations...
of carboxyhemoglobin due to continued smoking may be responsible for that segment of the polycythemic population which fails to respond to therapy with supplemental oxygen.6

In an effort to determine the role of carboxyhemoglobin in the response to therapy with supplemental oxygen, we compared the effect of such therapy in polycythemic smokers and nonsmokers with severe hypoxia.

**MATERIALS AND METHODS**

Patients seen in the Pulmonary Function Laboratory of the Veterans Administration Hospital, Tampa, Fla, in the one-year period between April 1975 and April 1976 were routinely evaluated. This evaluation included measurements of the hemoglobin level, carboxyhemoglobin level, and percent arterial oxygen saturation (SaO2) determined by a spectrophotometric oximeter (Instrumentation Laboratory CO-Oximeter 182) by methods previously described.9 The SaO2 was also calculated from the PaO2 and pH using a blood gas calculator. The SaO2 determined by the spectrophotometric oximeter is the ratio of the level of oxyhemoglobin divided by the sum of the levels of oxyhemoglobin, carboxyhemoglobin, and reduced hemoglobin. Other measurements of SaO2 use the ratio of the oxyhemoglobin level divided by the levels of reduced hemoglobin and oxyhemoglobin and, thus, do not take carboxyhemoglobin into account. Samples of arterial blood were also analyzed for the PaO2, arterial carbon dioxide tension (PaCO2), and pH by an acid-base digital analyzer (radiometer PBM 72). The hematocrit reading was determined on spun samples of arterial or venous blood in most patients. Previous studies in our laboratory have shown no significant difference between arterial and venous hematocrit readings (unpublished observations). Those patients with a measured SaO2 less than or equal to 93 percent and a hematocrit reading greater than or equal to 54 percent without another known cause for secondary polycythemia were termed polycythemic from oxygen desaturation and were selected for further study.

In this manner, 18 patients were shown to have polycythemia and were further evaluated. Spirometric studies, including determinations of the forced vital capacity and the forced expiratory volume in one second (FEV1), were performed, and a questionnaire regarding smoking was completed. The normal spirometric values were those of Kory et al.10 A complete blood cell count, including determination of the platelet count, was performed in the Clinical Pathology Laboratory of the VA Hospital. Levels of arterial blood gases were determined with the patient in the sitting position and then after being supine for 20 minutes. A sample of venous blood was obtained for measuring the level of 2,3-diphosphoglycerate and was analyzed according to the method of Beutler.11 Determinations of the mass of red blood cells and the volume of plasma were performed in 13 of the 18 patients according to the method of Hurley.12 Determinations of the partial pressure of oxygen at which hemoglobin is 50 percent desaturated (P50) were performed with the use of a spectrophotometric oximeter (Instrumentation Laboratory CO-Oximeter 182), a blood gas analyzer (Instrumentation Laboratory model 241), and a tomodensitometer (Instrumentation Laboratory model 237). Three 5-ml aliquots of arterial blood treated with heparin were used to plot the SaO2 at 50 percent saturation determined as the P50 at 37°C and pH 7.40.13

Patients were evaluated for the adequacy of their medical therapy by one of us (L.J.F.), and when indicated, changes were made, and the patients were restudied after six weeks. Patients who smoked were encouraged to stop smoking. Patients who successfully discontinued smoking were followed-up and repeat studies were performed after six weeks. No changes were made in medical therapy during the period of administration of oxygen. Hypoxic patients with a PaO2 less than or equal to 65 mm Hg who were unable to discontinue smoking and nonsmoking patients with a PaO2 less than or equal to 65 mm Hg were placed on 24-hour continuous therapy with supplemental oxygen. Oxygen was administered through nasal prongs utilizing an "H" tank for nocturnal therapy and a portable-walker apparatus (Linde Walker) or "E" tank during waking hours. The amount of oxygen given was determined in the laboratory as the rate of flow sufficient to maintain a PaO2 greater than or equal to 65 mm Hg in both the supine and upright positions, when possible. This has previously been shown to be the approximate PaO2 below which polycythemia begins to occur.14 Compliance to the appropriate rate of flow was verified through the records of the oxygen supplier. Patients were appropriately advised about the hazards of smoking around oxygen.

**RESULTS**

Eighteen patients were shown to have polycythemia during the period of study. An obese nonsmoker developed a normal hematocrit reading after optimization of his medical therapy, including reduction of his weight. Another patient had hereditary hemorrhagic telangiectasia and a large pulmonary arteriovenous malformation. His hematocrit reading, PaO2, and SaO2 returned to normal after surgical removal of the malformation. Two smokers were able to stop smoking and reversed their polycythemia while increasing their values for PaO2 and SaO2.

Fourteen patients received therapy with supplemental oxygen. Three of the nonsmokers used oxygen for insufficient periods of time (less than six hours per day) and failed to respond. Reasons given by the patients for failure to use the oxygen as prescribed included the discomfort of nasal prongs, fear of addiction, fear of use while asleep, inconvenience during periods of activity, and social stigma attached to the apparatus.

The remaining 11 patients were further studied (Table 1). The results before and at least six weeks after therapy with supplemental oxygen are shown in Table 2. The five nonsmokers had a mean carboxyhemoglobin level of 3 ± 0.5 percent and responded to therapy with supplemental oxygen with a decrease in the mean hematocrit reading from 57 ± 2 percent to 48 ± 2 percent (P < 0.0025). With therapy with supplemental oxygen, the mean PaO2 in nonsmokers increased from 53 ± 2 mm Hg to 69 ± 2 mm Hg (P < 0.01), and the measured SaO2 increased from 86 ± 2 percent to 94 ± 1 percent (P < 0.0025). The carboxyhemoglobin level with
therapy with supplemental oxygen in nonsmokers was 2 ± 0.4 percent and was not significantly different from values before treatment (P > 0.05).

Six smokers with a carboxyhemoglobin level of 13 ± 2 percent before therapy responded to administration of supplemental oxygen with a decrease in the hematocrit reading from 62 ± 1 percent to 57 ± 1 percent (P < 0.0025). With therapy with supplemental oxygen, the mean PaO2 in smokers increased from 53 ± 3 mm Hg to 69 ± 3 mm Hg (P < 0.0005), while the measured SaO2 increased from 82 ± 2 percent to 88 ± 1 percent (P < 0.01). The carboxyhemoglobin level with therapy with supplemental oxygen was 10 ± 2 percent in smokers and was not significantly different from values before therapy (P > 0.05).

The mean values for PaO2 in the two groups were not different before or after therapy with supplemental oxygen (P > 0.49). Although the baseline values for measured SaO2 were similar for the two

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### Table 2—Results Before and at Least Six Weeks After Therapy with Oxygen in Hypoxic Polycythemic Smokers and Nonsmokers*

<table>
<thead>
<tr>
<th>Data</th>
<th>Smokers (n = 6)</th>
<th>Nonsmokers (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit reading, percentage</td>
<td>62 ± 1</td>
<td>57 ± 1</td>
</tr>
<tr>
<td>PaO2, mm Hg</td>
<td>53 ± 3</td>
<td>69 ± 3</td>
</tr>
<tr>
<td>PaCO2, mm Hg</td>
<td>54 ± 5</td>
<td>53 ± 3</td>
</tr>
<tr>
<td>Carboxyhemoglobin level, percent</td>
<td>13 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>SaO2, percent</td>
<td>82 ± 2</td>
<td>88 ± 1</td>
</tr>
<tr>
<td>Measured**</td>
<td>87 ± 3</td>
<td>91 ± 1</td>
</tr>
</tbody>
</table>

*Table values are means ± 1 SE.

**Determined by spectrophotometric oximeter.

†Determined by blood gas calculator.

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groups (P > 0.05), smokers had lower values for measured SaO2 with therapy with supplemental oxygen (P < 0.0005). The smokers had significantly higher hematocrit readings both before and after therapy (P < 0.01). The response to therapy with supplemental oxygen was less dramatic in the smokers in spite of comparable baseline values for PaO2 and comparable increases in PaO2 with therapy with supplemental oxygen. Carboxyhemoglobin levels were significantly higher in the smokers than the nonsmokers, both before and after therapy with supplemental oxygen (P < 0.0025). As can be seen from Table 3, there was no significant difference in mean values for the level of 2,3-diphosphoglycerate and P50 between smokers, nonsmokers, and normal volunteers (P > 0.05).

### Discussion

It has long been recognized that some patients respond to chronic hypoxia with the development of secondary polycythemia. This is believed to be a compensatory response to tissue hypoxia that improves delivery of oxygen by increasing the arterial oxygen content as a result of the increase in the mass of red blood cells. Because polycythemia secondary to hypoxia implies a decrease in the delivery of oxygen to the tissues, it is thought to be a reliable

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### Table 3—Levels of 2,3-Diphosphoglycerate and P50 before Therapy with Oxygen*

<table>
<thead>
<tr>
<th>Data</th>
<th>2,3-Diphosphoglycerate Level, μmol/gm of Hemoglobin</th>
<th>P50, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers (n = 6)</td>
<td>14.2 ± 0.4</td>
<td>24.0 ± 0.8</td>
</tr>
<tr>
<td>Nonsmokers (n = 5)</td>
<td>15.3 ± 1.4</td>
<td>25.6 ± 0.3</td>
</tr>
<tr>
<td>Normal volunteers (n = 13)</td>
<td>15.2 ± 0.5</td>
<td>25.3 ± 0.3</td>
</tr>
</tbody>
</table>

*Table values are means ± 1 SE.

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the postulation of the role of carboxyhemoglobin.8

Patients who smoke and who inhale carbon monoxide from combustion of tobacco may decrease the delivery of oxygen to their tissues by the following three mechanisms: (1) carbon monoxide binds to a portion of the molecule of hemoglobin to form carboxyhemoglobin, which occupies some of the otherwise available sites for binding of oxygen; (2) carbon monoxide causes a leftward shift of the oxyhemoglobin dissociation curve; and (3) carbon monoxide can reduce the PaO2.8

Recently, a group of patients has been described with reversible secondary polycythemia from chronic oxygen desaturation without hypoxia. These patients had elevated carboxyhemoglobin levels with normal values for PaO2, and the polycythemia was reversed with cessation of smoking.7 Although polycythemia is an uncommon occurrence in smokers (incidence estimated to be between 1 and 5 percent), a knowledge of this cause of polycythemia may have major therapeutic implications.7 If it is correct to assume that oxygen desaturation caused by elevated carboxyhemoglobin concentrations would be unresponsive to therapy with supplemental oxygen, it would be important to determine the carboxyhemoglobin level in patients being evaluated for possible therapy with oxygen as a treatment for secondary polycythemia. The present study was undertaken to determine the role of carboxyhemoglobin in the response of hypoxic polycythemic smokers to therapy with supplemental oxygen.

The response to therapy with supplemental oxygen was compared in polycythemic hypoxic nonsmokers and polycythemic hypoxic smokers. From the results in the two groups (six smokers and five nonsmokers), it can be seen that both smokers and nonsmokers responded to therapy with supplemental oxygen with an increase in the SaO2 and a decrease in the hematocrit reading; however, the response in the smokers was less dramatic, despite comparable baseline values for PaO2 and comparable increases in PaO2 with therapy with supplemental oxygen. The significantly lower values for SaO2 seen in the smokers before and after therapy with supplemental oxygen reflect the additional desaturation from elevated concentrations of carboxyhemoglobin.

Values for oxygen desaturation were determined in this study by the spectrophotometric oximeter. This instrument is particularly suited for determining oxygen saturation in smokers. Not only can the carboxyhemoglobin level be determined directly, but the saturation obtained reflects the influence of carboxyhemoglobin. Classic methods of determining oxygen saturation assume that all hemoglobin is available for binding oxygen and, thus, will give higher levels because of failure to take carboxyhemoglobin into account. Saturation determined by the spectrophotometric oximeter represents the fraction of total sites on hemoglobin that are combined with oxygen. Saturation is shown in Table 2 both as measured from the spectrophotometric oximeter and as calculated from the PaO2 and pH using a standard blood gas calculator, which is the most common way to determine SaO2 in most clinical laboratories. The measured and calculated values for SaO2 were not significantly different before and after therapy with oxygen in the nonsmokers; however, in the smokers the calculated values for SaO2 were higher before and after therapy with oxygen, since they do not reflect the influence of carboxyhemoglobin.

Another method of measuring SaO2 is to determine the ratio of the oxyhemoglobin level divided by the sum of the levels of reduced hemoglobin and oxhemoglobin and, thus, represents actual measured saturation in terms of hemoglobin available for binding with oxygen. In Table 2, the SaO2 of smokers before therapy with oxygen is 82 percent of the total hemoglobin. Considering that 13 percent of the hemoglobin is bound by carbon monoxide and is unavailable for binding with oxygen, then the remaining hemoglobin available to bind oxygen (87 percent) is actually 94 percent saturated. In the nonsmokers the SaO2 is 86 percent of total hemoglobin. Since only 3 percent of the hemoglobin is bound by carbon monoxide, the remaining hemoglobin (97 percent) is 88 percent saturated. Thus, saturation in terms of the hemoglobin available for binding with oxygen was lower in the nonsmokers, and there was a greater potential for response to therapy with oxygen in the nonsmokers.

Attempts were made to exclude other factors which might influence the varying response to therapy with oxygen. Levels of arterial blood gases were not significantly different in the two groups in the supine or the upright position. In addition, the rates of flow were determined to be sufficient to maintain a PaO2 greater than or equal to 65 mm Hg in both the supine and upright positions. Because of varia-
bility of the carboxyhemoglobin level and PaO₂ throughout the day and night, it was impossible to exactly quantitate the contribution of each to polycythemia. It is conceivable, although unlikely, that the smokers had more significant nocturnal hypoxia; however, this was not possible for us to investigate. Compliance with the prescribed therapy with oxygen was assessed by interviewing the patient, as well as by reviewing the records of the company supplying the oxygen. We, therefore, believe that smoking, with its consequent carboxyhemoglobinemia, does account for the incomplete response to therapy with supplemental oxygen in smokers.

Certain therapeutic implications in the management of patients with secondary polycythemia can be drawn from this study. First, patients should be thoroughly evaluated for reversible medical or surgical causes of polycythemia. It is possible that with more vigorous medical treatment of an underlying condition or surgery to correct a right-to-left shunt, chronic hypoxia will improve sufficiently to reverse the secondary polycythemia and, thus, alleviate the need for administration of supplemental oxygen. Secondly, a history of smoking and preferably a determination of the carboxyhemoglobin level should be obtained. Additional studies, such as measurements of the level of 2,3-diphosphoglycerate and P₅₀, did not aid in predicting the response to therapy with supplemental oxygen and probably are unnecessary. Patients with elevated carboxyhemoglobin concentrations should be encouraged to discontinue smoking. In some instances, this alone will reverse the secondary polycythemia. Patients who are hypoxic and polycythemic despite optimal medical therapy and have normal carboxyhemoglobin levels show an excellent response to therapy with supplemental oxygen. Patients who are hypoxic and polycythemic but continue to smoke and have elevated carboxyhemoglobin concentrations respond incompletely to therapy with supplemental oxygen. In addition to smoking, a poor response may be due to poor compliance in “taking” the prescribed therapy with oxygen. If therapy with supplemental oxygen is used in smokers, it is imperative that the patient be carefully instructed and warned of the dangers of smoking around oxygen. If any doubt exists as to the patient’s adherence to standards of safety, therapy with supplemental oxygen should not be used.

REFERENCES