Hyperbilirubinemia Does Not Interfere with Hemoglobin Saturation Measured by Pulse Oximetry

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This prospective clinical study evaluated the influence of high bilirubin plasma levels on the Nellcor® pulse oximeter readings (SpO₂). Twenty-nine icteric patients (mean total bilirubin 19.2 mg/dl, range 2.3-84.3 mg/dl) were compared with 46 controls. The difference between SpO₂ and oxyhemoglobin percentage of hemoglobin (HbO₂corr) or fractional saturation as measured by a seven wavelengths Corning Co 2500 Co-oximetry® and corrected for the spectral error induced by hyperbilirubinemia in that co-oximeter was greater in icteric patients (bias and precision: 2.9% ± 2.2% vs. 1.7% ± 2.7%, P < 0.03). However, icteric patients had also higher corrected carboxyhemoglobin levels (CoHbcorr) (1.8% ± 0.7% vs. 1.3% ± 0.8%, P < 0.005) due to production of carbon monoxide during the catalysis of hemoglobin. Pulse oximeters read most of CoHb as oxyhemoglobin. After correcting SpO₂ for carboxyhemoglobin in both groups of patients, the 95% confidence limits from the obtained regression line were the same in icteric patients (−0.81%, 1.08%) as in controls (−0.89%, 1.08%). There was thus no demonstrable direct influence of high bilirubin plasma levels on SpO₂ as measured by a Nellcor® pulse oximeter. (Key words: Blood, hemoglobin; oxyhemoglobin; Monitoring, pulse oximetry: bilirubin.)

Pulse oximetry provides a rapid and accurate assessment of arterial hemoglobin oxygen saturation (SpO₂). Since its introduction several causes of interference have been identified. These include severe vasoconstriction, electrocautery, patient movement, high carboxyhemoglobin levels, iv dyes, and high intensity light or heat lamps. Data are contradictory regarding the influence of high bilirubin plasma levels upon SpO₂. Taylor and Whitwam stated that hyperbilirubinemia causes underestimation of the true saturation, whereas Ramanathan et al., in a nonrelated study, reported no influence of bilirubin levels up to 14 mg/dl upon SpO₂. We undertook a prospective clinical study to quantify the influence of bilirubin on SpO₂, with special attention being paid to the interference of bilirubin with the co-oximeter used as reference.

Methods

A total of 75 adult patients were prospectively studied. They were divided in two groups according to their clinical appearance (jaundice). Bilirubin was greater than 2.3 mg/dl (36 μM) in patients in group 1 (29 icteric patients) and less than 1.5 mg/dl in patients in group 2 (controls). The causes of jaundice were cirrhosis in eight patients, massive transfusion and hemolysis in eight, congenital biliary atresia in five, sepsis in four, and acute Wilson’s disease, pulmonary embolism, chronic heart failure, and bile duct carcinoma in one patient each. The control group (group 2) had 46 patients. Seven patients in group 1 and two in group 2 were studied two or three times on different days and under different clinical conditions. A total of 87 measurements were thus performed in the operating room, the recovery room, or the intensive care unit. All the patients had an indwelling arterial catheter inserted as part of their clinical management.

The following procedure was applied for each measurement. The DS 100 A adult finger probe of a Nellcor® N100 Pulse Oximeter® (Nellcor Incorporated, Hayward, California) was placed on a finger of the limb on which the arterial catheter was inserted. The displayed value of SpO₂ was recorded if the heart rate did not differ by more than three beats from the heart rate on an ECG monitor (Nellcor instruction manual). An arterial blood sample was then drawn into a heparinized syringe and analyzed immediately. PaO₂, PaCO₂, pH, and SaO₂ were measured without correction for patient’s temperature using a Corning 175 Blood Gas Analyzer® while Hbtot, MetHb, CoHb, and HbO₂ were measured with a seven-wavelength co-oximeter (Corning CO 2500®, Medfield, Massachusetts). This apparatus hemolyzes blood by high frequency ultrasonic vibration before processing it to the optical measurement system. It recalibrates itself automatically every 30 min and its performance characteristics have been described elsewhere.** The influence of high levels of bilirubin (up to 49 mg/dl) on this co-oximeter has been studied in our laboratory by Clerboux et al. who proposed an equation correcting HbO₂, MetHb, and CoHb readings.

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TABLE 1. Summary of Patients’ Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1: 29 Iscemic Patients; 38 Measurements</th>
<th>Group 2: 46 Control Patients; 49 Measurements</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>36.7 ± 24.1 (0.7–71)</td>
<td>38.9 ± 25.2 (0.5–75)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.0 ± 25.3 (7.9–90.0)</td>
<td>54.7 ± 27.6 (4.6–100.0)</td>
<td>NS</td>
</tr>
<tr>
<td>PacO2 (mmHg)</td>
<td>82 ± 38 (39–159)</td>
<td>94 ± 50 (40–202)</td>
<td>NS</td>
</tr>
<tr>
<td>PacO2 (mmHg)</td>
<td>35 ± 5 (25–47)</td>
<td>38 ± 6 (29–61)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>pH (mmol/L)</td>
<td>36.3 ± 4.4 (28.8–47.8)</td>
<td>39.9 ± 6.0 (29.5–61.7)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Hbcat (g/dl)</td>
<td>11.0 ± 1.1 (7.9–12.9)</td>
<td>12.3 ± 1.8 (8.5–18.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>36.6 ± 0.5 (35.5–38.3)</td>
<td>36.2 ± 0.7 (34.0–37.5)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>19.2 ± 18.6 (2.3–84.3)</td>
<td>0.6 ± 0.4 (0.2–1.5)</td>
<td>NR</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>16.1 ± 17.2 (0.5–82.8)</td>
<td>0.2 ± 0.2 (0.0–0.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>35.5 ± 3.5 (0.4–19.0)</td>
<td>0.4 ± 0.3 (0.1–1.3)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Results are mean ± SD (range in parentheses) of all the measurements performed in both groups and statistical significance of differences. NS = not significant; NR = not relevant.

TABLE 2. Corrected and Uncorrected Patients’ Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1: 29 Iscemic Patients; 38 Measurements</th>
<th>Group 2: 46 Control Patients; 49 Measurements</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoHb (%)</td>
<td>2.4 ± 1.0 (1.1–5.7)</td>
<td>1.3 ± 0.8 (0.4–4.8)</td>
<td>NR</td>
</tr>
<tr>
<td>CoHbcorr (%)</td>
<td>1.8 ± 0.7 (0.8–3.6)</td>
<td>1.3 ± 0.8 (0.4–4.8)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>MetHb (%)</td>
<td>1.9 ± 1.3 (0.6–6.8)</td>
<td>1.1 ± 0.4 (0.0–2.2)</td>
<td>NR</td>
</tr>
<tr>
<td>MetHbcorr (%)</td>
<td>1.3 ± 0.6 (0.5–5.2)</td>
<td>1.1 ± 0.4 (0.0–2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>HbO2 (%)</td>
<td>91.4 ± 5.0 (70.3–96.3)</td>
<td>90.8 ± 7.5 (68.0–99.0)</td>
<td>NS</td>
</tr>
<tr>
<td>HbO2corr (%)</td>
<td>91.9 ± 5.1 (70.0–97.3)</td>
<td>90.6 ± 7.5 (68.0–99.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Spo2 (%)</td>
<td>95 ± 5 (71–100)</td>
<td>92 ± 8 (67–100)</td>
<td>NS</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>95.2 ± 4.5 (79–99.1)</td>
<td>93 ± 6.9 (74–99.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Spo2 – HbO2 (%)</td>
<td>3.4 ± 2.5 (~1.3–10.7)</td>
<td>1.7 ± 2.7 (~3.7–19.9)</td>
<td>NR</td>
</tr>
<tr>
<td>Spo2 – HbO2corr (%)</td>
<td>2.9 ± 2.2 (~2.7–18.9)</td>
<td>1.7 ± 2.7 (~3.7–19.9)</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Results are mean ± SD (range in parentheses) of all the measurements performed in both groups and statistical significance of differences. HbO2, CoHb, and MetHb values reported are those read on the Corning 2500 co-oximeter without correction for hyperbilirubinemia. HbO2corr, CoHbcorr, and MetHbcorr are corrected for the spectral error induced by hyperbilirubinemia in that co-oximeter. NS = not significant; NR = not relevant.

According to total bilirubin level at different HbO2 values. These corrected values will be called HbO2corr, MetHbcorr, and CoHbcorr, respectively. The method of Jendraski and Grof was used to measure direct and total bilirubin levels on an Autoanalyzer.††

Statistical Analysis

Comparisons between the two groups were performed using Student’s t tests or Mann-Whitney’s rank-sum tests according to the result of Shapiro’s test for normality. Results were expressed as the mean ± SD and range. Corrections of measurements were established by stepwise linear regression analysis. The nonparametric Kendall (tau) and Spearman (r) rank correlation coefficients were also computed to confirm the statistical association between variables. Finally, corrected measurements were compared with Student’s paired t test or Wilcoxon rank signed test. All tests were two tailed. A P value greater than 0.05 was considered to be statistically not significant: in that case the null hypothesis cannot be rejected. All tests were performed with BMDP statistical software.‡‡

Results

The results of all measured variables are given in tables 1 and 2. Corrected and uncorrected values of HbO2, CoHb, and MetHb are provided. Individual values of Spo2 versus HbO2 are plotted in figure 1. Due to hemolysis or surgical bleeding, anemia was more common in patients in the jaundiced group, but, within the observed range of values of Hbtot, no influence on HbO2 reading is ex-


pected. Icteric patients also had a higher pH and a lower PaCO₂. Clinically unimportant although statistically significant differences in body temperature also existed between groups.

Bias (mean difference between SpO₂ and HbO₂corr) was significantly greater in icteric patients than in controls (2.9% vs. 1.7%, P < 0.03), although the range of differences was large in both groups. Precision (or SD) was approximately the same: 2.2% in icteric patients versus 2.7% in controls. Figure 2 shows the relationship between bias (SpO₂ - HbO₂corr) and total bilirubin level.

Icteric patients had a significantly higher CoHbcorr level (1.8% ± 0.7% vs. 1.3% ± 0.8%, P < 0.005) despite a possible underestimation in our series because of their relative hyperventilation (lower PaCO₂) and despite the presence of smokers among the control patients. However, CoHbcorr was poorly correlated to total bilirubin level: CoHbcorr = 0.0163 total B + 1.529, r = 0.42 (Bravais-Pearson: P < 0.01; Spearman and Kendall: P < 0.02). Corrected MetHb levels were not significantly different in the two groups (1.3% ± 0.8% vs. 1.1% ± 0.4%).

Using the values measured in the icteric patients, we derived an equation correcting as SpO₂corr the SpO₂ displayed by the Nellcor® pulse oximeter:

$$SpO₂corr = SpO₂ - 1.06CoHbcorr - 0.92$$

where CoHbcorr is the CoHb level measured by a Corning Co 2500® co-oximeter and corrected for the spectral error due to hyperbilirubinemia. In icteric patients bias between SpO₂corr and HbO₂corr was 0.11% with a precision of 2.07%. In controls bias between SpO₂corr and HbO₂corr was 0.09% (precision, 2.57%). Figure 3 shows the remaining differences between SpO₂corr and HbO₂corr as a function of total bilirubin level. The 99% confidence limits of SpO₂corr - HbO₂corr were −0.81% to 1.03% from the calculated regression line in icteric patients and −0.89% to 1.08% in controls. In controls the 95% prediction limits for a given SpO₂ (for a given SpO₂, how accurately can we predict HbO₂?) were ±5.4% without correction for CoHb and ±5.0% after correction for CoHb. In icteric patients the 95% prediction limits for SpO₂corr were ±4.2%.

**Discussion**

Before discussing the results of our study, an important point needs to be made about the terminology used.⁵
Many papers compare $\text{SpO}_2$ with the so-called functional hemoglobin saturation, \textit{i.e.},

$$
100 \times \frac{\text{HbO}_2}{\text{Hb} + \text{HbO}_2}
$$

In principle functional hemoglobin saturation should equal $\text{SaO}_2$ as computed in the blood gas apparatus.\textsuperscript{5} When using $\text{SaO}_2$ or functional hemoglobin saturation the influence of CoHb and MetHb is not considered. Although of little importance when studying healthy nonsmoking volunteers this becomes relevant in clinical practice, as shown in our series by the difference between $\text{SaO}_2$ and $\text{HbO}_2\text{corr}$ because CoHb and MetHb reduce the amount of hemoglobin effectively available for oxygen transport. We therefore compared $\text{SpO}_2$ with the fractional hemoglobin saturation, \textit{i.e.},

$$
100 \times \frac{\text{HbO}_2}{\text{Hb} + \text{HbO}_2 + \text{CoHb} + \text{MetHb}}
$$

as measured by a cooximeter. Our results in controls are comparable to previous publications comparing the Nellcor\textsuperscript{6} $\text{SpO}_2$ with fractional hemoglobin saturation.\textsuperscript{9} Bilirubin could affect the clinical validity of $\text{SpO}_2$ monitoring by direct photometric interference or by an indirect mechanism related to CoHb production. Concerning the photometric interference, the oxyhemoglobin absorption curve peaks at approximately 415, 560, and 590 nm. The spectrum of bilirubin has a broad single peak around 460 nm.\textsuperscript{10} In one of the patients with a total bilirubin level of 60 mg/dl, spectrophotometry revealed that this peak extended far beyond this value and up to 650 nm with the absorbance of bilirubin exceeding by far that of the various forms of hemoglobin. Despite this, from a theoretical point of view, interference of bilirubin with $\text{SpO}_2$ is unlikely. Pulse oximetry uses 660 nm and 940 nm wavelengths to measure the pulse-added absorbance of light through a vascular bed and converts it into a plethysmographic waveform at each wavelength. The ratio of the amplitude of these plethysmographic signals is then processed in an algorithm to calculate $\text{SpO}_2$.

Hyperbilirubinemia might also influence pulse oximetry by an indirect mechanism. Bilirubin and carbon monoxide are formed in equimolar amounts during the catabolism of hemoglobin, when the porphyrin ring is split into bile pigments, thus increasing CoHb level.\textsuperscript{11} However, this level is variable for any given total bilirubin level because it is higher in hemolytic than in obstructive jaundice and depends on exogenous factors such as smoking, oxygen therapy, and artificial ventilation. The difference between $\text{SpO}_2$ and $\text{HbO}_2\text{corr}$ was significantly greater in icteric patients. They also had significantly higher CoHbcorr levels. Statistical correlation between CoHbcorr level and total bilirubin remains poor because CoHb is also under the influence of exogenous factors as stated above. Most of carboxyhemoglobin is read as saturated hemoglobin by pulse oximeters.\textsuperscript{2,12} When correcting the $\text{SpO}_2$ displayed for the true CoHb level (CoHbcorr in icteric patients) bias and precision were comparable in icteric and control groups, and the 99% confidence limits from the calculated regression lines were similar. Therefore, the null hypothesis "bilirubin per se does not interfere with pulse oximetry" cannot be rejected.

The influence of methemoglobin on $\text{SpO}_2$ is more complex as it varies with HbO2 and MetHb.\textsuperscript{13,14} As the MetHbcorr levels measured in the icteric patients were rather low and not significantly different from those measured in controls, methemoglobin probably had no major influence in our series. However, care must be taken in individual patients because many drugs (\textit{e.g.}, nitroglycerin, lidocaine) may elevate MetHb levels and thus influence $\text{SpO}_2$. Whether the difference between $\text{SpO}_2$ and $\text{HbO}_2\text{corr}$ is influenced by the absolute value of HbO2 could not be evaluated because only a few values were below 85% HbO2.

The validity of the equation derived from our results to correct the $\text{SpO}_2$ displayed by the Nellcor\textsuperscript{®} pulse oximeter according to the CoHb level measured by the Corning Co 2500\textsuperscript{®} co-oximeter and corrected for hyperbilirubinemia remains to be established in a prospective group.

To conclude, pulse oximetry retains all its value as a clinical monitoring device in icteric patients provided a determination of HbO2, CoHb, and MetHb is carried out with a co-oximeter and corrected for the bilirubin-induced spectral error of that co-oximeter to enable the clinician...
to appreciate the importance of $\text{SpO}_2 - \text{HbO}_2$ for each patient. We could not demonstrate any influence of bilirubin by itself on Nellcor® $\text{SpO}_2$.

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References