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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 (Sp_{O_2}). 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 Sp_{O_2} and oxyhemoglobin percentage of hemoglobin (Hb_{O_2}corr) or fractional saturation as measured by a seven wavelengths Corning Co 2500 Co-oximeter® 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 catabolism of hemoglobin. Pulse oximeters read most of CoHb as oxyhemoglobin. After correcting Sp_{O_2} for carboxyhemoglobin in both groups of patients, the 99% confidence limits from the obtained regression line were the same in icteric patients (−0.81%, 1.03%) as in controls (−0.89%, 1.08%). There was thus no demonstrable direct influence of high bilirubin plasma levels on Sp_{O_2} as measured by a Nellcor® pulse oximeter. (Key words: Blood, hemoglobin: oxyhemoglobin saturation; carboxyhemoglobin. Monitoring, pulse oximetry: bilirubin.)

PULSE OXIMETRY provides a rapid and accurate assessment of arterial hemoglobin oxygen saturation (Sp_{O_2}).[1] Since its introduction several causes of interference have been identified. These include severe vasoconstriction, electrocautery, patient movement, high carboxyhemoglobin levels,[2] iv dyes,[3] and high intensity light or heat lamps.[4] However, data are contradictory regarding the influence of high bilirubin plasma levels upon Sp_{O_2}.[5] Taylor and Whitwam stated that hyperbilirubinemia causes underestimation of the true saturation,[6] whereas Ramanathan *et al.*, in a nonrelated study, reported no influence of bilirubin levels up to 14 mg/dl upon Sp_{O_2}.[7] We undertook a prospective clinical study to quantify the influence of bilirubin on Sp_{O_2}, with special attention being paid to the interference of bilirubin with the co-oximeter used as reference.[8]

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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 100A 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 Sp_{O_2} 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. Pa_{O_2}, Pa_{CO_2}, *p*H, and Sa_{O_2} were measured without correction for patient's temperature using a Corning 175 Blood Gas Analyzer® while Hbtot, MetHb, CoHb, and HbO_2 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 Clerbaux *et al.*[8] who proposed an equation correctingHb_{O_2}, MetHb, and CoHb readings

** Clerbaux T, Willems E, Nullens W, Brasseur L: Performance characteristics of the Co-oximeter Corning 2500 with respect to reference methods. Proceedings of the IV Mediterranean Conference on Medical and Biological Engineering. Sevilla, Spain, September 9–12, 1986, pp 613–614.

TABLE 1. Summary of Patients' Data

	Group 1: 29 Icteric Patients; 38 Measurements	Group 2: 46 Control Patients; 49 Measurements	P
Age (yr)	36.7 ± 24.1 (0.7–71)	38.9 ± 25.2 (0.3–75)	NS
Weight (kg)	50.0 ± 25.3 (7.9–80.0)	54.7 ± 27.6 (4.6–100.0)	NS
Pa_{O_2} (mmHg)	82 ± 23 (39–153)	94 ± 50 (40–202)	NS
Pa_{CO_2} (mmHg)	35 ± 5 (25–47)	38 ± 6 (29–61)	<0.02
$[H^+]$ (neq/l)	36.3 ± 4.4 (28.8–47.9)	39.9 ± 6.0 (29.5–61.7)	<0.02
Hb_{tot} (g/dl)	11.0 ± 1.1 (7.9–12.9)	12.3 ± 1.8 (8.5–18.0)	<0.001
Temperature (°C)	36.6 ± 0.5 (35.5–38.3)	36.2 ± 0.7 (34.0–37.5)	<0.003
$Bilirubin_{tot}$ (mg/dl)	19.2 ± 18.6 (2.3–84.3)	0.6 ± 0.4 (0.2–1.5)	NR
$Bilirubin_{dir}$ (mg/dl)	16.1 ± 17.2 (0.5–82.8)	0.2 ± 0.2 (0.0–0.8)	NR
$Bilirubin_{indir}$ (mg/dl)	3.5 ± 3.5 (0.4–19.0)	0.4 ± 0.3 (0.1–1.3)	NR

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

	Group 1: 29 Icteric Patients; 38 Measurements	Group 2: 46 Control Patients 49 Measurements	P
CoHb (%)	2.4 ± 1.0 (1.1–5.7)	1.3 ± 0.8 (0.4–4.8)	NR
CoHbcorr (%)	1.8 ± 0.7 (0.8–3.6)	1.3 ± 0.8 (0.4–4.8)	<0.005
MetHb (%)	1.9 ± 1.3 (0.6–6.8)	1.1 ± 0.4 (0.0–2.2)	NR
MetHbcorr (%)	1.3 ± 0.8 (0–3.2)	1.1 ± 0.4 (0.0–2.2)	NS
Hb_{O_2} (%)	91.4 ± 5.0 (70.3–96.3)	90.6 ± 7.5 (68.0–99.0)	NS
Hb_{O_2}corr (%)	91.9 ± 5.1 (70.0–97.3)	90.6 ± 7.5 (68.0–99.0)	NS
Spo_2 (%)	95 ± 5 (71–100)	92 ± 8 (67–100)	NS
Sa_{O_2} (%)	95.2 ± 4.5 (79–99.1)	93 ± 6.9 (74–99.7)	NS
$Spo_2 - Hb_{O_2}$ (%)	3.4 ± 2.5 (−1.3–+10.7)	1.7 ± 2.7 (−3.7–+9.9)	NR
$Spo_2 - Hb_{O_2}$corr (%)	2.9 ± 2.2 (−2.7–+8.9)	1.7 ± 2.7 (−3.7–+9.9)	<0.03

Results are mean ± SD (range in parentheses) of all the measurements performed in both groups and statistical significance of differences. Hb_{O_2}, CoHb, and MetHb values reported are those read on the Corning 2500® co-oximeter without correction for hyperbilirubinemia. Hb_{O_2}corr, 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 Hb_{O_2} values. These corrected values will be called Hb_{O_2}corr, MetHbcorr, and CoHbcorr, respectively. The method of Jendrasik and Grof was used to measure direct and total bilirubin levels on an Autoanalyser.††

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 Hb_{O_2}, CoHb, and MetHb are provided. Individual values of Spo_2 *versus* Hb_{O_2} 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 Hb_{O_2} reading is ex-

†† The measurements and fractionation of bilirubin on the Autoanalyzer by the method of Jendrasik and Grof. Automation in Analytic Chemistry. Technicon Symposium 1964.

‡‡ BMDPC, Statistical Software (1987 release): Department of Biomathematics, University of California. Edited by Dixon WJ. Los Angeles, UCLA Press, 1987.

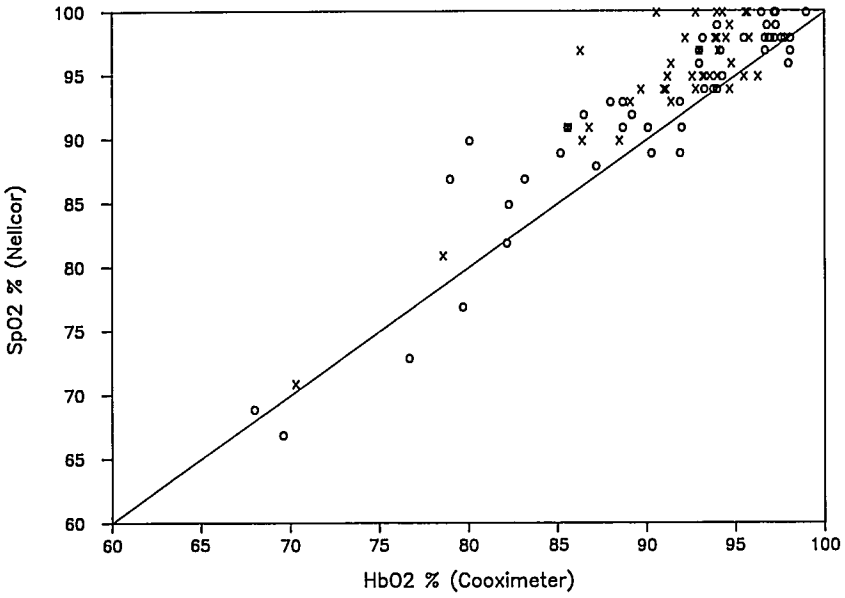

FIG. 1. Individual values of Sp_{O_2} plotted against Hb_{O_2} in icteric (x, n = 38) and control patients (o, n = 49); line of identity is indicated. Hb_{O_2} values are not corrected for the spectral error due to bilirubin on the Corning 2500® co-oximeter.

pected. Icteric patients also had a higher *p*H and a lower Pa_{CO_2}. Clinically unimportant although statistically significant differences in body temperature also existed between groups.

Bias (mean difference between Sp_{O_2} and Hb_{O_2}corr) 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 ($Sp_{O_2} - Hb_{O_2}$corr) 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 Pa_{CO_2}) 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 Sp_{O_2}corr the Sp_{O_2} displayed by the Nellcor® pulse oximeter:

$$Sp_{O_2}corr = Sp_{O_2} - 1.06CoHbcorr - 0.92$$

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 Sp_{O_2}corr and Hb_{O_2}corr was 0.11% with a precision of 2.07%. In controls bias between Sp_{O_2}corr and Hb_{O_2} was 0.09% (precision, 2.57%). Figure 3 shows the remaining differences between Sp_{O_2}corr and Hb_{O_2}corr as a function of total bilirubin level. The 99% confidence limits of Sp_{O_2}corr − Hb_{O_2}corr 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 Sp_{O_2} (for a given Sp_{O_2}, how accurately can we predict Hb_{O_2}?) were ±5.4% without correction for CoHb and ±5.0% after correction for CoHb. In icteric patients the 95% prediction limits for Sp_{O_2}corr were ±4.2%.

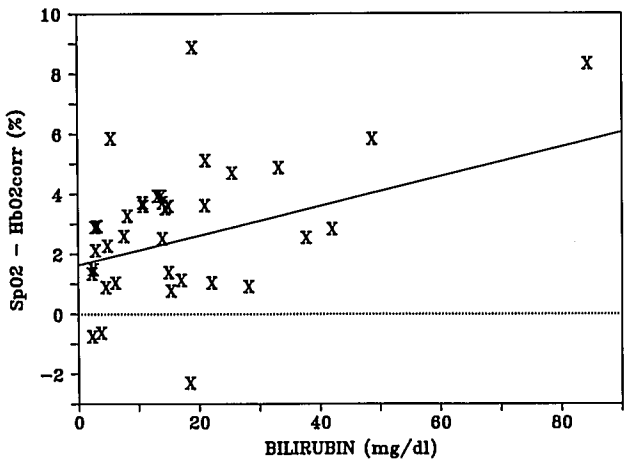

FIG. 2. $Sp_{O_2} - Hb_{O_2}$corr in percent saturation, as a function of total bilirubin level; individual values. The line was obtained by regression analysis. $Sp_{O_2} - Hb_{O_2}$corr = 1.751 + 0.048B; $r = 0.44$; $P < 0.008$.

Discussion

Before discussing the results of our study, an important point needs to be made about the terminology used.[5]

Many papers compare Sp_{O_2} with the so-called functional hemoglobin saturation, *i.e.*,

$$\frac{100 \times Hb_{O_2}}{Hb + Hb_{O_2}}$$

In principle functional hemoglobin saturation should equal Sa_{O_2} as computed in the blood gas apparatus.[5] When using Sa_{O_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 Sa_{O_2} and Hb_{O_2}corr because CoHb and MetHb reduce the amount of hemoglobin effectively available for oxygen transport. We therefore compared Sp_{O_2} with the fractional hemoglobin saturation, *i.e.*,

$$\frac{100 \times Hb_{O_2}}{Hb + Hb_{O_2} + CoHb + MetHb}$$

as measured by a cooximeter. Our results in controls are comparable to previous publications comparing the Nellcor® Sp_{O_2} with fractional hemoglobin saturation.[9] Bilirubin could affect the clinical validity of Sp_{O_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.[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 Sp_{O_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 Sp_{O_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.[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 Sp_{O_2} and Hb_{O_2}corr was significantly greater in icteric patients. They also had significantly higher CoHbcorr levels. Statistical correlation between

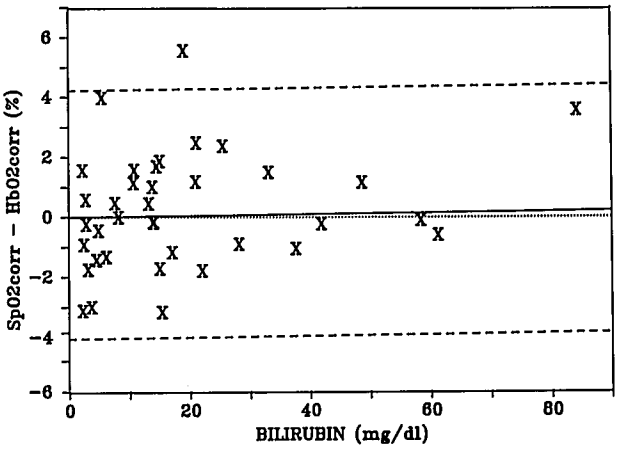

FIG. 3. Sp_{O_2}corr − Hb_{O_2}corr in percent saturation, as a function of total bilirubin level; individual values. Line of regression: Sp_{O_2}corr − Hb_{O_2}corr = 0.0206B − 0.302; r = 0.18; NS and 95% prediction limits (– – –).

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.[2,12] When correcting the Sp_{O_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 Sp_{O_2} is more complex as it varies with Hb_{O_2} and MetHb.[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 (*e.g.*, nitroglycerin, lidocaine) may elevate MetHb levels and thus influence Sp_{O_2}. Whether the difference between Sp_{O_2} and Hb_{O_2} (or Hb_{O_2}corr) is influenced by the absolute value of Hb_{O_2} could not be evaluated because only a few values were below 85% Hb_{O_2}.

The validity of the equation derived from our results to correct the Sp_{O_2} displayed by the Nellcor® pulse oximeter according to the CoHb level measured by the Corning Co 2500® 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 Hb_{O_2}, 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 $Sp_{O_2} - Hb_{O_2}$ for each patient. We could not demonstrate any influence of bilirubin by itself on Nellcor® Sp_{O_2}.

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References

1. Mihm FG, Halperin BD: Noninvasive detection of profound arterial desaturation using a pulse oximetry device. ANESTHESIOLOGY 62:85–87, 1985
2. Barker SJ, Tremper KK: The effect of carbon monoxide inhalation on pulse oximetry and transcutaneous PO_2. ANESTHESIOLOGY 66:677–679, 1987
3. Scheller MS, Unger RJ, Kelner MJ: Effects of intravenously administered dyes on pulse oximetry readings. ANESTHESIOLOGY 65:550–552, 1986
4. Brooks TD, Paulus DA, Winkle WE: Infrared heat lamps interfere with pulse oximeters. ANESTHESIOLOGY 61:630, 1984
5. Payne JP, Severinghaus JW: Pulse Oximetry. Berlin-Heidelberg. Springer-Verlag, 1986
6. Taylor MB, Whitwam JG: The current status of pulse oximetry. Anaesthesia 41:943–949, 1986
7. Ramanathan R, Durand M, Larrazabai C: Pulse oximetry in very low birth weight infants with acute and chronic lung disease. Pediatrics 79:612–617, 1987
8. Clerbaux T, Willems E, Nullens W, Baele PL, Veyckemans F, Hassoun A: Interference de la bilirubine sur la saturation oxyhemoglobinee mesuree par voie photometrique. Nouv Press Med 17:960, 1988
9. Kagle DM, Alexander CM, Berko RS, Giuffre M, Gross JB: Evaluation of the Ohmeda 3700 pulse oximeter. ANESTHESIOLOGY 66:376–380, 1987
10. Amazon K, Soloni F, Arkadi MR: Separation of bilirubin from hemoglobin by recording derivative spectrophotometry. Am J Clin Pathol 75:519–523, 1981
11. Engel RR, Rodkey FL, Krill CE: Carboxyhemoglobin levels as an index of hemolysis. Pediatrics 47:723–730, 1971
12. Mertzlufft F, Zander R: Non-invasive oximetry using the Biox III oximeter: Clinical evaluation and physiological aspects, Pulse Oximetry. Edited by Payne JP, Severinghaus JW. Berlin-Heidelberg. Springer-Verlag, 1986, pp 71–77
13. Barker SJ, Tremper KK, Hyatt J, Zaccari J: Effects of Methemoglobinemia on pulse oximetry and mixed venous oximetry (abstract). ANESTHESIOLOGY 67:A171, 1987
14. Eisenkraft JB: Pulse oximeter desaturation due to methemoglobinemia. ANESTHESIOLOGY 68:279–282, 1988