VALIDATION OF REFLECTANCE PULSE OXIMETRY: AN EVALUATION OF A NEW SENSOR IN PIGLETS

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ABSTRACT. Objective. A new reflectance pulse oximetry sensor, developed for intrapartum estimation of arterial oxygen saturation (SaO_2), was calibrated and evaluated. The sensor contains two light emitting diodes of 735 and 890 nm, and a photodetector at a distance of 14 mm from both light emitting diodes. **Methods.** In seven Yorkshire/Hampshire piglets, the reflectance sensor (Nellcor Puritan Bennett Inc.) was calibrated using blood sample SaO_2 values. The resulting calibration line was evaluated in four Dutch piglets, by comparing pulse oximetry saturation readings (SpO_2) with blood sample and intravascular fiberoptic oximetry SaO_2 values. Several reflectance sensors were fixed on each animal. Desaturation levels were obtained by changing the gas mixture of oxygen/nitrous oxide via a tracheal catheter. **Results.** In the Yorkshire/Hampshire piglets, the standard deviation of difference ($SpO_2 - SaO_2$) was 4.7% ($n = 364$), over an SaO_2 range of 17% to 100%. In the Dutch piglets, the mean difference ($SpO_2 - SaO_2$) was −1.6% and the standard deviation of difference was 5.4%, over the same SaO_2 range ($n = 254$). Comparisons of continuous recordings of reflectance SpO_2 and fiberoptic SaO_2 revealed variation in individual regression lines. **Conclusions.** This new 735/890 nm reflectance sensor demonstrates acceptable accuracy in piglets. A further evaluation during labor should assess its feasibility for fetal surveillance.

KEY WORDS. Arterial oxygen saturation, reflectance pulse oximetry, validation, pig.

INTRODUCTION

Pulse oximetry has become a standard technique to monitor the arterial oxygen saturation (SaO_2) in critically ill patients during anesthesia and intensive care. With the development of a reflectance sensor this technique might be equally useful during labor. The first experimental reflectance sensors used the same light emitting diodes (LEDs) as the commercial transmission sensors, namely 660 nm for the red LED and 890 nm to 940 nm for the infrared light [1]. Optimism rose when it appeared possible to monitor the fetus for prolonged periods during labor with reported pulse oximetry saturation values (SpO_2) between 10% and 80% [2–4]. Early animal validation studies indicated a reasonable accuracy over this SaO_2 range [5–7]. However, we could not confirm the reported accuracy for the Nellcor 660/890 nm sensor [8]. Moreover, this sensor was highly inaccurate when it was placed over a subcutaneous vein on the fetal lamb scalp and during an adrenalin induced vasoconstriction [9]. Inaccuracies were also observed during labor, when two sensors were placed simultaneously on

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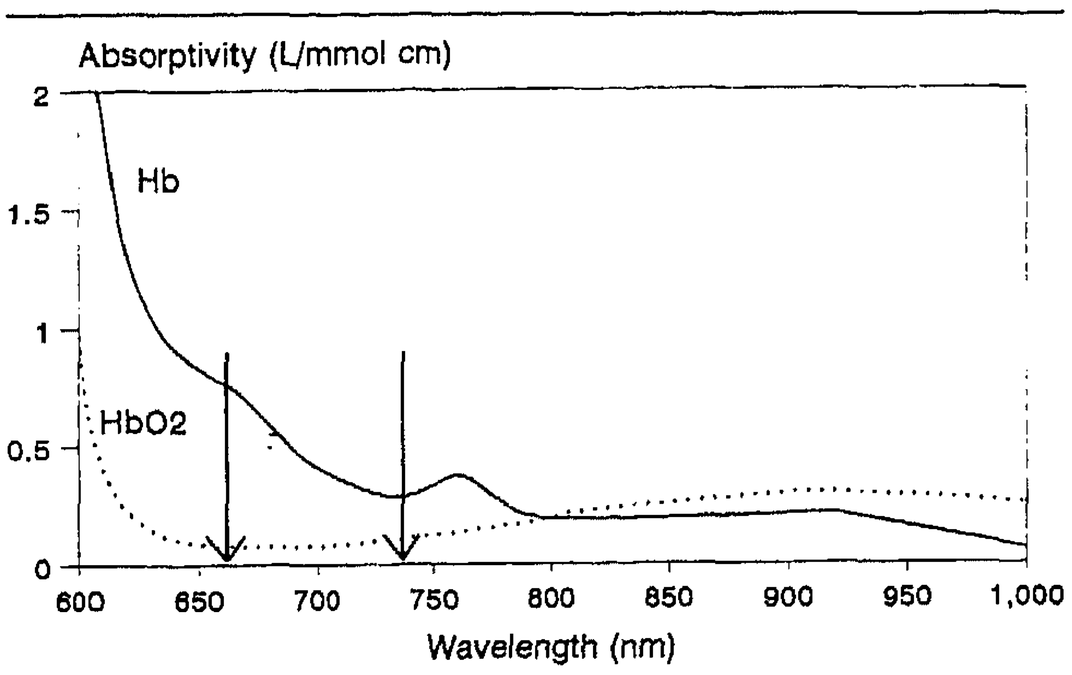

Fig. 1. Absorbance spectrum, HbO_2: oxyhemoglobin, Hb: deoxyhemoglobin. Arrows indicate 660 nm and 735 nm wavelengths.

the fetus. Differences in SpO_2 values up to 30% between the two sensors were repeatedly observed [10]. Consequently, alternative approaches in sensor design should be considered for intrapartum use.

Pulse oximeters use a fixed empirically derived calibration curve for the relation between the SaO_2 and the ratio of the relative pulse sizes for red and infrared light. As a consequence, variations in the relationship caused by differences in light propagation between subjects or locations, cannot be taken into account. Such variations are caused, for instance, by different blood volume fractions in the transilluminated tissue, or different coefficients for light scattering. At high SaO_2 levels, influences of blood volume fractions are predicted to be of minor importance for the calibration [11,12]. However, at low SaO_2 levels, when red light is significantly more attenuated by deoxyhemoglobin in the tissue than infrared light (Figure 1), the influence of different blood volume fractions becomes significant [11,12]. It is therefore a reasonable explanation that the differences in light propagation between 660 nm and 890 nm has led to the observed inaccuracies.

Changing the wavelength from 660 nm to 735 nm (Figure 1) leads to less attenuation of the red light at low SaO_2 levels. In a theoretical Monte Carlo model based on both absorption and scattering of light, Mannheimer (Mannheimer P. et al., submitted) predicted a significantly better similarity of light propagation for a 735/890 nm combination of LEDs than for a 660/890 nm combination of LEDs. A prototype reflectance sensor with a combination of 735 and 890 nm LEDs, and with a photodetector at a distance of 10 mm from both LEDs, developed by Nellcor, yielded indeed much better results in piglets compared with the 660/890 nm sensor [13].

A new version of this prototype sensor has now been developed for intrapartum use, where the LED-photodetector distance is changed from 10 mm to 14 mm. Pilot studies revealed, that the 14 mm separation was less sensitive to perturbations caused by excessive applied force, compared to the 10 mm separation (data not published). Theoretically, the broader LED-photodetector separation de-emphasizes potential artifacts caused by perturbation to the uppermost tissue layers as the detected light tends to travel deeper. As validation is fundamental to this technique, we set out this study to validate this 735/890 nm reflectance sensor with a 14 mm LED-photodetector distance in piglets. The piglet was used because it has a skin structure akin to man [14]. The present study describes the calibration of the sensor in California in a first set of experiments, and thereafter an independent evaluation in The Netherlands in a second set of experiments. Furthermore, head and buttock locations were compared because different tissue characteristics may influence the calibration. Finally, stepwise desaturations were analyzed per animal and/or sensor location to gain insight into inter-subject and interposition variation in regression lines.

MATERIAL AND METHODS

Surgery

Eleven piglets were used in this study, after approval was obtained from the local ethical committees for animal experiments. In Richmond, California, seven piglets of the Yorkshire/Hampshire breed (age 1.5–13 weeks, weight 3–20 kg) were anesthetized using 2.8% isoflurane in a gas mixture of oxygen and nitrogen. When necessary, 0.5 mg pancuronium bromide was administered intravenously during the experiment. In Nijmegen, The Netherlands, four piglets of the Dutch breed (age 6–14 weeks, weight 7–26 kg) were anesthetized with 0.4–0.8% enflurane in the gas mixture of oxygen and nitrous oxide and with a continuous intravenous ketamine infusion at 200–300 mg/hour. After intubation of the piglets, desaturation levels were obtained by changing the gas mixture of oxygen and nitrous oxide. Rectal temperature was kept constant at 37.5 °C (range 36.5 °C to 39 °C) by covering the animal with a silver swaddling blanket and by placing a thermostatic heating pad underneath the animal. Electrocardiogram (ECG) electrodes were fixed subcutaneously. The carotid or brachial artery was cannulated for blood samples.

In the Dutch piglets, a fiberoptic catheter (Abbott Opticath®, U440, 4 French, Oximetrix Inc., Mt. View, CA) was inserted in the femoral artery, and positioned in the descending aorta. The fiberoptic catheter was connected to an Oximetrix computer (Oximetrix Inc.).

On the Yorkshire/Hampshire piglets four reflectance

sensors (Nellcor, Pleasanton, CA, USA) were fixed to the shaved skin of head (2 sensors) and buttock (2 sensors) and used simultaneously. In two of the animals the four sensors were placed on the head, buttock, groin and the cheek. One or two desaturations were performed in each animal. Sensors were held in place with a band at a controlled sensor-to-skin applied force. On the Dutch piglets two reflectance sensors were taped to the shaven skin. After each desaturation sensors were replaced to another side of the animal. In all four Dutch piglets a sensor was present on the head and buttock. In two animals the sensors were replaced on head and buttock positions only, and in two animals sensors were also placed on the groin or cheek. Three to four desaturations were performed in each animal. The sensors made satisfactory contact with the skin and optical shunting from one sensor towards a second sensor was not observed (disconnecting one of the sensors did not change the red and infrared pulses of the other pulse oximeter). The operation lights were turned off during the experiments.

Experiments

In all 11 piglets desaturations were achieved by a stepwise lowering of the fraction of inspired oxygen concentration from 25–30% to 6%, resulting in an SaO_2 range from 100% to 17%. In each animal samples were taken over the total SaO_2 range. The recovery period between each desaturation lasted 30 min. A total number of 12 desaturations was achieved in the seven Yorkshire/Hampshire piglets, resulting in a total of 48 desaturation recordings for the sensors used. In the Dutch piglets 14 desaturations were achieved, resulting in 28 desaturation recordings. During each desaturation approximately eight blood samples were obtained. Heparinized blood samples were drawn from the carotid or brachial artery after a 0.5 to 1 min period of SaO_2 stabilization.

Data analysis

The reflectance sensor contained a combination of 735 nm and 890 nm LEDs, which transilluminated the tissue, the 735 LED having less than 3% secondary emission. The photodetector was placed 14 mm from the two LEDs and received the backscattered light. All sensors together with the ECG-electrodes were connected to prototype fetal pulse oximeters (Nellcor Puritan Bennett Inc.). The pulse oximeter used the ECG to cardiosynchronize the red and infrared pulses (C-lock, Nellcor Puritan Bennett Inc). From the red and infrared pulses a red to infrared ratio was calculated. The pulse oximeter has a signal quality scale; the signal quality is defined for 0% to 100%, based on various factors such as pulse amplitude, synchrony of red and infrared waveform and synchrony with the ECG. All ratio values with a quality of more than 50% were accepted for analysis. Quality of the signal was $<50\%$ 19 times at the time of the blood sample (3.1% of total paired measurements).

Blood samples were analyzed within 5 min, or stored on ice and measured within 30 min using multi-wavelength photometers (IL482^{R} CO-Oximeter, Instrumentation Laboratories, Lexington, MA; ABL510^{TM}, Blood Gas System, Radiometer, Copenhagen, Denmark) corrected for pig blood. Sample SaO_2 values were used for comparison with the pulse oximetry data and to calibrate the fiberoptic saturation values off line in the range below 80%, as earlier described [15]. We excluded all paired data which would result in a pulse oximeter saturation reading of $\geq 100\%$, because a pulse oximeter will clip all values at 100% (eight points of the Yorkshire/Hampshire piglets and five points of the Dutch piglets; 2.1% of total paired measurements).

Statistics

In the Yorkshire/Hampshire piglets, the pulse oximeter red to infrared ratios (dependent variable) were related to the sample SaO_2 values (independent variable) by means of linear regression (least square method). This calculated ratio/SaO_2 regression line was used as a calibration line to convert the red to infrared ratios to pulse oximetry saturation readings (SpO_2), in all 11 piglets. The SaO_2/SpO_2 regression line of the Dutch piglets was compared with the SaO_2/SpO_2 regression line of the Yorkshire/Hampshire piglets (covariance analysis).

For the comparison of two methods measuring the same quantity it is recommended to calculate the mean difference (bias) and the standard deviation of the differences (precision) [16]. Paired measurements of SpO_2 and SaO_2 were analyzed separately for the Yorkshire/Hampshire and Dutch piglets, according to the recommended statistics.

Head and buttock measurements were compared by analyzing the mean bias of individual animals (Student's *t*-test).

In the Dutch piglets, all continuous fiberoptic recordings were compared with the continuous pulse oximeter recordings for the stepwise desaturation period below 80% SaO_2 (the expected upper limit of fetal SaO_2 values). The bias and the standard deviation of the residuals (SD_{res}, linear regression) were calculated as described above. The SD_{res} represents the random 'variability' and is equal to the precision if the bias is zero.

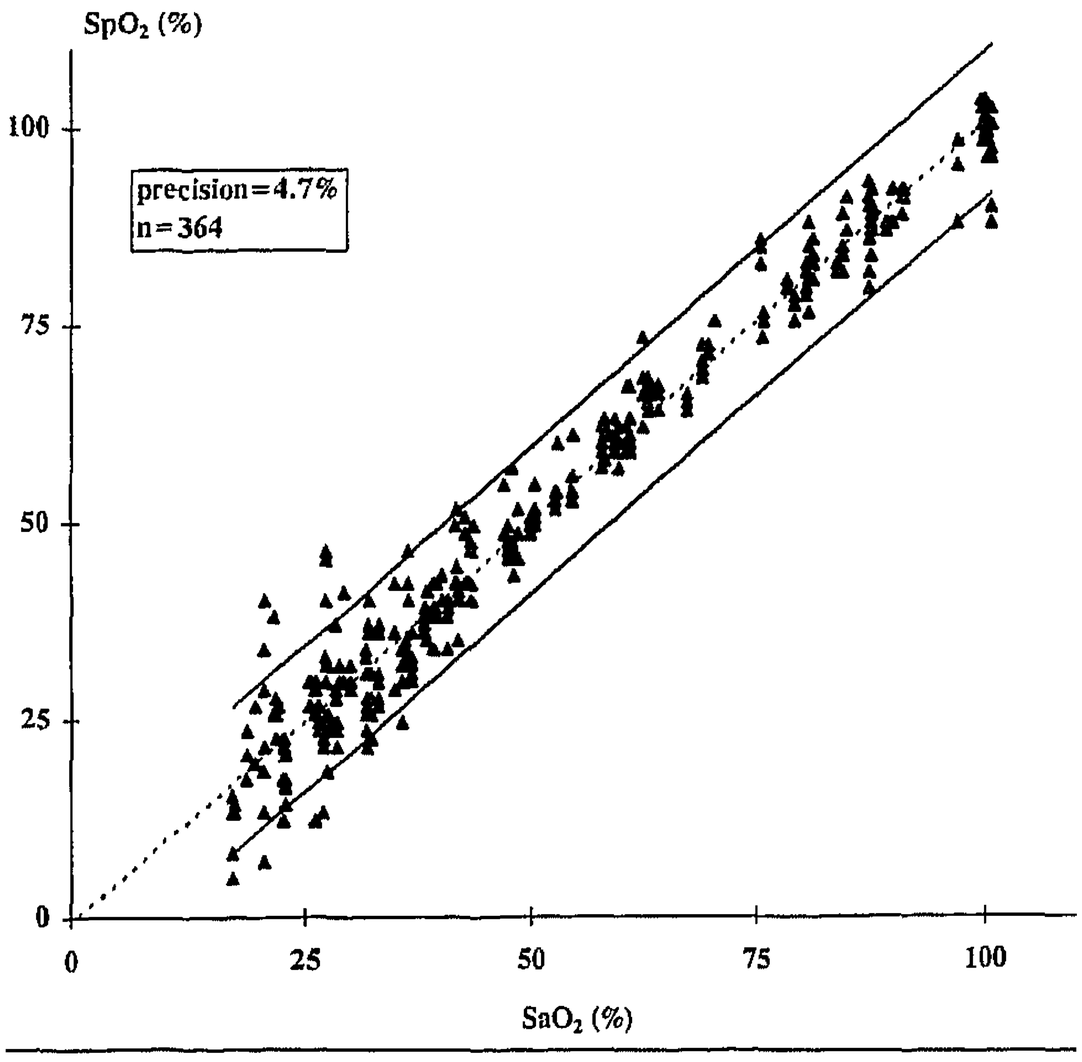

Fig. 2. Pulse oximeter SpO_2 values against the blood sample SaO_2 values with insertion of the 95% prediction interval in the 7 Yorkshire/Hampshire piglets. Dashed line is the line of identity.

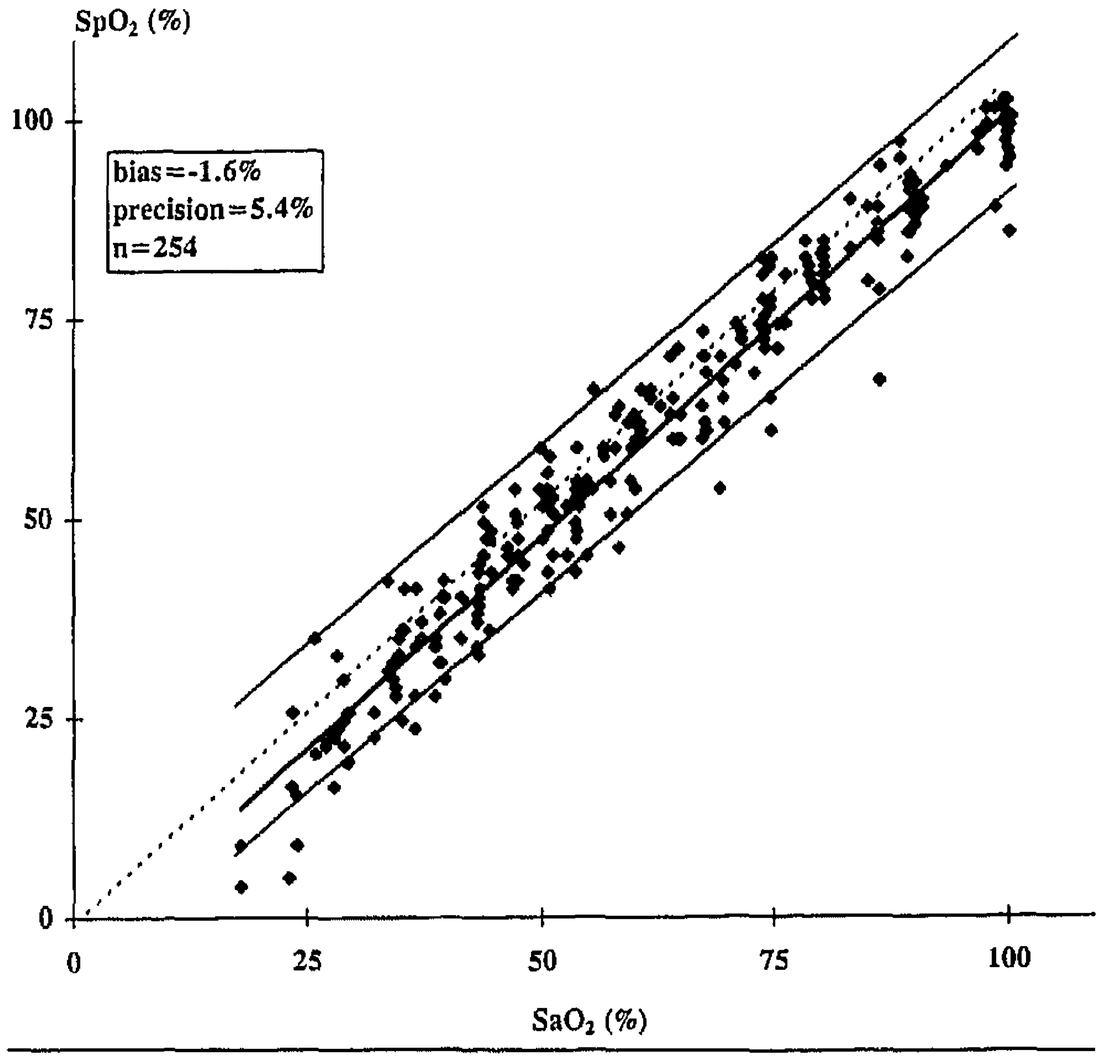

Fig. 3. Pulse oximeter SpO_2 values against the blood sample SaO_2 values for the 4 Dutch piglets with insertion of the 95% prediction interval for the Yorkshire/Hampshire piglets. Solid line is best fitting regression line for the Dutch piglets: $SpO_2 = 1.06 \cdot$ sample $SaO_2 - 5.31$. Dashed line is the line of identity.

Continuous recordings were averaged over a five second period.

Statistical significance was pronounced at a p-value <0.05.

RESULTS

A total number of 364 paired measurements of sample SaO_2 and SpO_2 readings were analyzed for the 7 Yorkshire/Hampshire piglets (Figure 2). The bias was 0 because the data were used to obtain the ratio/SaO_2 calibration line in these piglets. The precision was 4.7% over an SaO_2 range of 17% to 100%. The 95% prediction interval around the SpO_2/SaO_2 regression line was ± 9.4%.

In Figure 3, the paired measurements of sample SaO_2 and SpO_2 readings for the 4 Dutch piglets are shown. Measurements were obtained over the same SaO_2 range of 17% to 100%. The SpO_2/SaO_2 regression line was slightly, but significantly different from the SpO_2/SaO_2 regression line in the Yorkshire/Hampshire piglets (covariance analysis $p<0.001$). Of the 254 points, 91% fell within the 95% prediction interval based on the Yorkshire/Hampshire piglets. The best fitting regression line for the Dutch piglets was $SpO_2 = 1.06 \cdot$ sample $SaO_2 - 5.31$. The bias was −1.6% and the precision was 5.4%. A summary divided over different SaO_2 ranges is given in Table 1. The bias and precision improved both for the Yorkshire/Hampshire and the Dutch piglets, for SaO_2 values above 30%. Below 30% SaO_2, heart rate and blood pressure often decreased with concomitant ECG waveforms. Inclusion of SpO_2 values ≥100% did not change the results.

The bias per animal differed for both head and buttock measurements; e.g. for the head measurements in the Yorkshire/Hampshire piglets it ranged from −1.3% to +8.4% (median +0.6%). Overall, no difference was observed for the mean bias for head and buttock meas-

Table 1. Mean Difference (bias) and Standard Deviation of Differences (precision) of Pulse Oximeter SpO_2 Reading Minus Sample SaO_2 Value over Various SaO_2 Ranges, for Yorkshire/Hampshire and Dutch Piglets Separately; n = *number of paired measurements*

SaO_2 range	Bias	Precision	*n*
Yorkshire/Hampshire piglets			
17%–30%	0.1	7.2	75
31%–80%	0.2	3.9	200
17%–100%	0.0	4.7	364
Dutch piglets			
17%–30%	−6.3	6.6	24
31%–80%	−1.1	5.0	179
17%–100%	−1.6	5.4	254

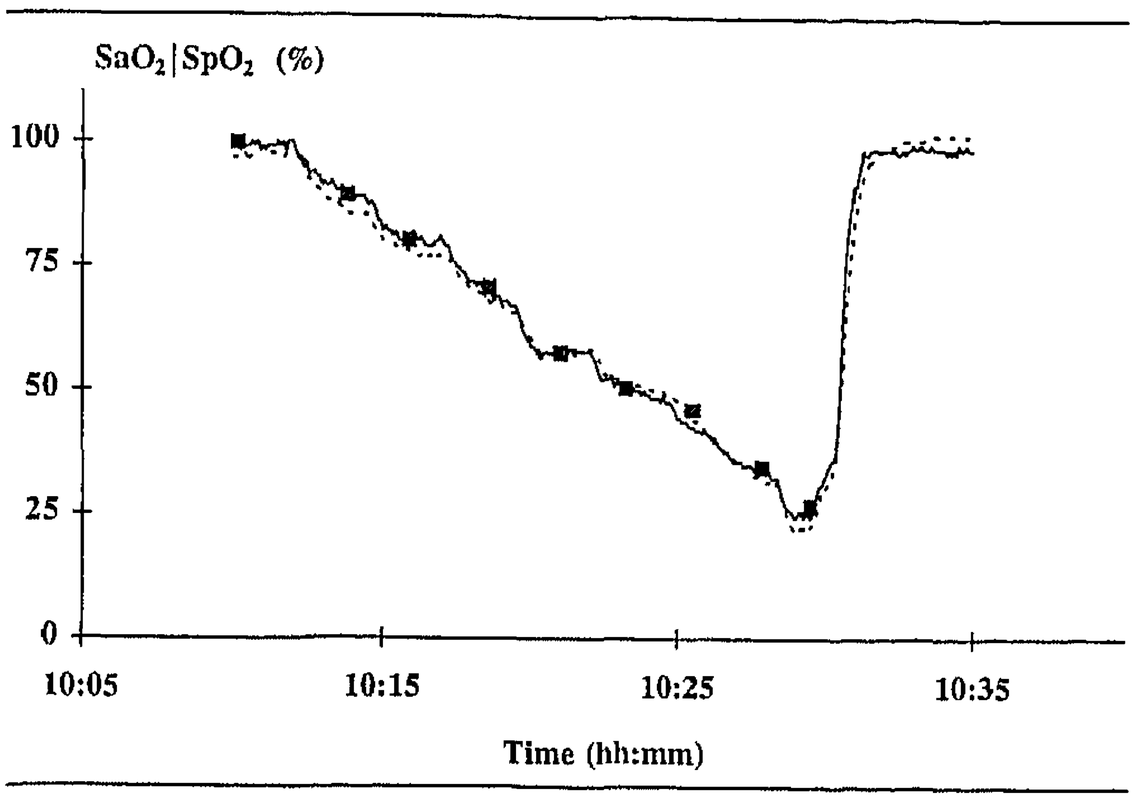

Fig. 4. Example of the first desaturation in Dutch piglet number 4 with the sensor on the head. Continuous recordings for fiberoptic SaO_2 (solid line), pulse oximeter SpO_2 (dashed line) and sample SaO_2 values (■) are shown.

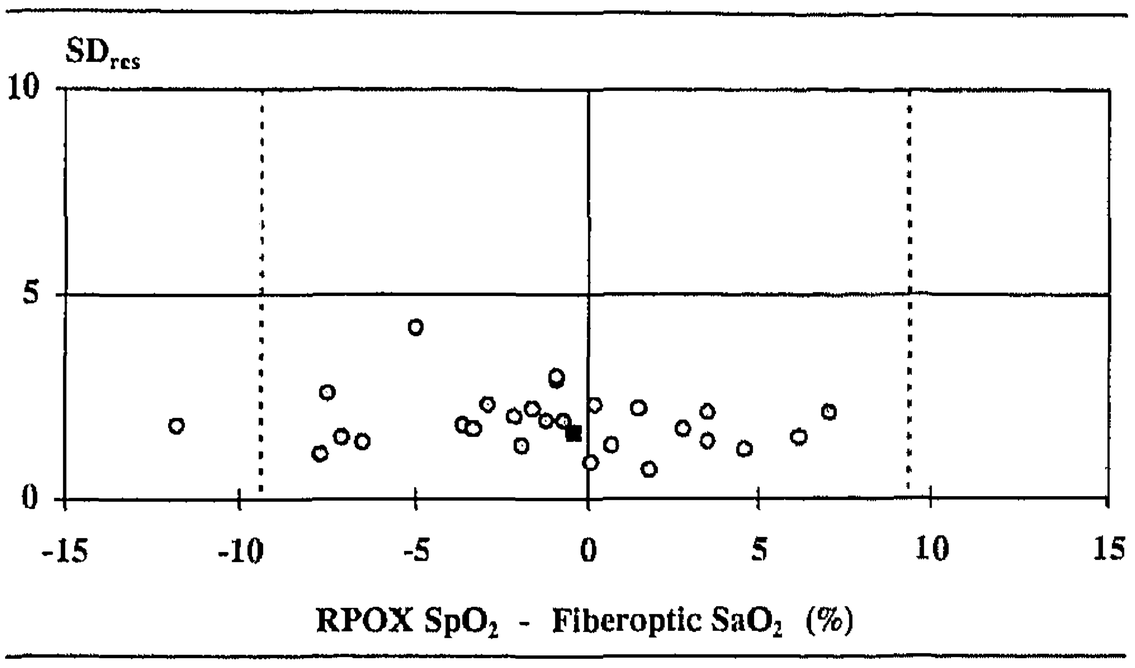

Fig. 5. Standard deviation of residuals (SD_{res}) against bias of 28 desaturations in 4 Dutch piglets for an SaO_2 value $<80\%$, with insertion of 95% prediction lines based on the Yorkshire/Hampshire piglets (dashed lines). Bias and SD_{res} are calculated during the stepwise desaturation period. The value of Figure 4 is marked with a square.

urements, in the Yorkshire/Hampshire piglets or in the Dutch piglets (Student's t-test $p > 0.05$).

For the Dutch piglets, continuous pulse oximetry SpO_2 recordings were compared with continuous fiberoptic SaO_2 recordings to gain insight into the data at a single position in the 4 piglets (inter-position differences). Off line calibration of the fiberoptic SaO_2 values resulted in an unbiased accurate continuous SaO_2 standard for comparison to the pulse oximeter SpO_2 readings; the standard deviation of residuals for the fiberoptic oximeter was $<2.5\%$ absolute. In Figure 4, an example of a stepwise desaturation in a Dutch piglet is given. The continuous recordings of the pulse oximetry SpO_2 and fiberoptic SaO_2, and sample values are shown. This pulse oximetry recording was very accurate and demonstrated a bias of -0.6% and an SD_{res} of $+1.6\%$, for the SaO_2 values below 80%. The bias and SD_{res} for the stepwise desaturation periods were calculated for each of the 28 desaturation recordings, below a fiberoptic SaO_2 value of 80%, and are shown together with the 95% prediction interval of the Yorkshire/Hampshire piglets in Figure 5. The mean difference of pulse oximetry SpO_2 and fiberoptic SaO_2 was generally within 5% absolute. Compared with the fiberoptic SaO_2, only one pulse oximetry SpO_2 recording had a bias outside the 95% prediction interval. This was a fourth desaturation with the sensor on the upper hindlimb. The SD_{res} values were below 5% for all recordings; inter-position data fell much closer to their linear regression lines than the pooled data, as shown in Figure 2 or Figure 3.

DISCUSSION

Reflectance pulse oximetry may become a useful additional technique for monitoring the fetal condition during labor. It is minimally invasive and easy to use. Moreover, the SaO_2 is an adequate oxygen parameter for the oxygen supply, because of the shape of the oxygen dissociation curve. Due to a relatively low fetal partial pressure for oxygen, a minor reduction in oxygen supply will lead to a detectable fall in fetal SaO_2. Before clinicians can rely on reflectance pulse oximetry, it should be extensively validated.

In the human fetus, double sensor studies can be performed by comparing two SpO_2 recordings. However, a reliable standard is necessary for a proper validation. Therefore arterial blood samples are needed, but these cannot be obtained in the human fetus during labor. The human adult is also not a suitable subject as it is unethical to perform hypoxemia studies with such low SaO_2 values. In critically ill neonates the SaO_2 may occasionally become as low as 60% [17] but this is still not low enough for the expected fetal SaO_2 range of 10% to 80% observed during labor (2–4). We therefore validated this new fetal reflectance sensor employing 735 and 890 nm LEDs and with a photodetector-LEDs distance of 14 mm in the piglet.

The pooled data of Figure 2 and Figure 3 exhibited a random "variability" (precision) of circa 5% in both groups of piglets. The small difference in regression lines between the two groups of piglets may have been caused by different species of piglets but is of no clinical importance. However, the single subject or single position data provided in general a much closer fit with their corresponding linear regression, shown by the smaller SD_{res} in Figure 4 and Figure 5. Much of the random variability of the pooled data is thus between-subject or between-

position rather than within-subject or within-position variability. This is also shown by the range of bias values (Figure 5). This between-subject variability does not become apparent if only a small number of animals is used with repeated measurements on the same position of the animal. Early animal validation studies used reflectance pulse oximetry with 660 nm sensors on two to four fetal lambs with repeated measurements on one position [5–7]. In our former study with the prototype 735/890 nm sensor we also found a precision of circa 5% in 6 piglets over an SaO_2 range of 18% to 100% [13]. The accuracy was better for SaO_2 values above 30% than for those below 30%. This level of 30% was chosen because our study in chronically instrumented fetal lambs indicated that metabolic acidosis started at this low SaO_2 level [18]. The new 735/890 nm reflectance pulse oximeter may be less accurate below 30% but a definitive conclusion cannot be based upon this study. The pulse amplitude of red and infrared signals decreased during the desaturation as a consequence of (sub)cutaneous vasoconstriction and led to a low signal to noise ratio, which will also occur during labor. However, heart rate and blood pressure also started to decrease with concomitant ECG waveforms at these low SaO_2 values, which are not necessarily apparent below 30% in the human fetus.

We could not observe a difference between measurements with sensors located at the head or the buttock for this combination of wavelengths. The tissue of the head consists of a relatively thin (sub)cutaneous layer with the bone of the cranium underneath, while the tissue of the buttock consists of a thicker (sub)cutaneous layer. With the 660/890 reflectance sensor we reported a difference between fetal lamb scalp and fetal lamb neck measurements [8].

We used the quality score of the pulse oximeter for the inclusion/exclusion beforehand. A quality value of 50% is often used during intrapartum use and was considered adequate. This quality score is not yet fully evaluated. However, it avoided the need for the observer to apply inclusion or exclusion criteria at the moment of analysis, with the possibility of accompanying bias.

Several factors have been recognized to influence the results of reflectance pulse oximetry, such as malpositioning of the sensor [19], improper data analysis [20], pressure on the sensor [21] and hair. In this study, sensors had an appropriate contact with the shaven skin, avoiding optical shunting of red or infrared light directly towards the photodetector [19]. All the displayed SpO_2 values were based on acceptable red and infrared pulses, which were in phase with each other and with the heart rate [20]. Increasing the pressure on the sensor has shown to improve the accuracy of reflectance pulse oximetry on the forehead of adults [21]. In our experiments, sensors were held in place by a small pressure on the sensor, by tape or a band, but we did not quantify the pressure needed.

The piglet, with a skin structure akin to man, provides an easy and adequate animal model in which the performance of reflectance pulse oximetry systems can be studied. Using 11 piglets with several sensors on various positions of the animal will give an appropriate estimation of the precision of this 735/890 nm sensor, for intrapartum use. However, small differences in the light absorption characteristics of hemoglobin in the spectral range, and differences in scattering characteristics of erythrocyte shape, skin and subcutaneous tissue between mammals, might lead to a different calibration line for the human fetus. This problem cannot yet be overcome by using *in vitro* models or complex theoretical models which incorporate both absorption and scattering characteristics, because a homogeneous medium is used which is a simplification of the heterogeneous medium of skin and subcutaneous tissue [11, 12, 22]. Nevertheless, evaluating the piglet calibration line in nine sick neonatal human infants over a blood sample SaO_2 range of 50% to 92% did not reveal a different calibration line (bias = −1.1%, precision = 5.4%, $n = 27$ in nine neonates) [23]. Comparing two simultaneously obtained SpO_2 recordings, in 27 human fetuses during labor, indicated a SD for a single sensor of 4.1% over a SpO_2 range of 30% to 60% [10].

Although *in vitro* models and complex theoretical models which incorporate absorption and scattering cannot be used for calibration of a new reflectance pulse oximetry system, they do provide a quantitative support for the estimation of the SaO_2 in various circumstances. The theoretical models have shown that the red to infrared ratio is influenced by optical characteristics (e.g. LED wavelength and LED-photodetector distance) as well as tissue characteristics e.g. blood volume, hematocrit [11, 12, 22]. The 660/940 nm reflectance sensor was highly inaccurate in the fetal SaO_2 range if the aforementioned characteristics were changed [11, 12]. Such calculations have not yet been published for this 735/890 nm reflectance sensor with a 14 mm LED-photodetector. Further animal studies and theoretical studies have to be performed before a definitive conclusion can be drawn that this new 735/890 nm reflectance pulse oximetry system is always reliable.

In conclusion, this new 735/890 nm reflectance sensor demonstrates acceptable accuracy in piglets. Further evaluations during labor should assess its feasibility for fetal surveillance.

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