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Transmission Pulse Oximetry in the Fetal Lamb: Is There a Universal Calibration?

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ABSTRACT

Transmission pulse oximetry is widely used for oxygen monitoring. The use of pulse oximeters is steadily expanding toward situations with low arterial oxygen saturation (Sao_2) values. Therefore, we evaluated transmission pulse oximetry in the unanesthetized fetal lamb at low Sao_2 levels. In seven fetal lambs, fetal hypoxemia was induced by occlusion of the maternal common iliac artery, four days after the instrumentation of the animal. Two Nellcor prototype transmission Y-sensors (light emitting diodes: 660 and 890 nm) were applied, one around a forelimb muscle and one around a skinfold in the neck, and were connected to Nellcor pulse oximeters. The pulse oximeter was calibrated for the skin measurements. Pulse oximeter saturation readings (Spo_2) were compared with sample Sao_2 values, over an Sao_2 range of 13 to 63%. For the neck sensor the SD of the difference was 5.0% (n = 101). For the muscle sensor the mean difference was 19.5% and the SD of the difference was 5.9% (n = 206). Regression analysis showed a different calibration line for the muscle sensor with the equation: $Spo_2 = 0.92 \cdot Sao_2 + 21.90$. Continuous recordings were obtained both from the forelimb muscle and from the neck, but the recordings from the neck showed a substantial loss of signal during the hypoxemia period. We conclude that transmission pulse oximetry is less accurate below an Sao_2 of 70% in fetal lambs than above 70% Sao_2. At these low levels of Sao_2, pulse oximeters may need to be constructed with different calibration lines for various application positions of the body. (***Pediatr Res* 39: 464–469, 1996**)

Abbreviations
LED, light emitting diode
Sao_2, arterial oxygen Hb saturation
SD_{res}, SD of residuals
Spo_2, pulse oximeter saturation reading

Transmission pulse oximetry is a precise method used for the continuous monitoring of Sao_2 in neonates, older infants, and adults, mostly in an Sao_2 range of 70 to 100% (1–5). Although pulse oximetry is not explicitly validated at low Sao_2 levels, the use of this technique is steadily expanding toward situations in which the Sao_2 is below 70%: during labor (6, 7), in the delivery room immediately after birth (8–10), and for the early detection of respiratory depression (11). Fetal Sao_2 values are predominantly below 70%.

Only a few studies have determined the accuracy of transmission pulse oximetry below 70% Sao_2. It is unethical to perform controlled studies of induced severe hypoxemia in humans. Animal models are therefore used to estimate the accuracy of transmission pulse oximetry for low Sao_2 values. These animal experiments showed a decreasing accuracy of transmission pulse oximetry for low Sao_2 values (12–14). In all of those studies commercial pulse oximeters were used with a calibration algorithm derived from experiments in healthy adults in an Sao_2 range from 70 to 100%, and this algorithm can probably not be extrapolated to lower Sao_2 values. Furthermore, commercial sensors often have small differences in spectral characteristics, which may influence the calibration below 70% (15).

In this study we set out to determine the accuracy of transmission pulse oximetry below 70% Sao_2 in the unanesthetized fetal lamb. Hypoxemia was induced by occluding the maternal blood flow to the uterus. Because the calibration of transmission pulse oximetry is sensitive to small differences in wavelengths between sensors, we used transmission pulse oximetry sensors with identical spectral characteristics (LED, 660 and 890 nm) and prototype oximeters developed for small fetal pulses.

METHODS

Surgery. For this study we used seven pregnant ewes of the Dutch Texel breed between 119 and 126 d of gestation (term 147 d). Food and water supply before and after surgery were given according to the rules of the animal laboratory. Anesthesia was induced with 30 mg/kg pentobarbital with 0.5%

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atropine i.v. and was maintained with 2.0% enflurane in a 2:1 mixture of nitrous oxide and oxygen, 0.5 L/min of each (closed system ventilation, Engström ER 300 respirator, Bromma, Sweden).

The abdomen was opened through a paramedian incision, after which the uterus was temporarily lifted out of the pelvis and covered with soaked gauzes. The peritoneum was opened over the trifurcation of the aorta into the common internal iliac artery and the external iliac arteries. A flexible inflatable occluder (diameter 8 or 10 mm, Rhodes Medical Instruments, Woodland Hills, CA) was placed around the common internal iliac artery. The uterus was then returned to the abdomen.

The fetal lamb was approached by hysterotomy above the fetal head. Three ECG electrodes were sutured s.c. on the sternum, right shoulder, and left side of the neck. Polyvinyl catheters (inner diameter 0.8 mm, outer diameter 1.6 mm) were inserted into a carotid artery, a jugular vein, and the amniotic cavity. A left forelimb was exteriorized and a muscle was prepared. A transmission pulse oximetry sensor (prototype, Dura Y-sensor, Nellcor Inc., Pleasanton, CA) was placed in a stainless steel support around the muscle leaving 7 mm of space between the LED and the photodiode. A second transmission sensor was placed around a skinfold left or right in the neck, contralateral to the catheterized carotid artery. The sensors made satisfactory contact with the tissue without applying excessive pressure to prevent compression of circulation. The uterus was then closed, and all electrodes and catheters were exteriorized through a skin incision in the ewe's flank and packed into a pouch on the ewe's back. Before the skin was closed 10^6 IU of penicillin were administered into the peritoneal cavity.

On the day of operation and during the recovery period antibiotics were administered daily: streptomycin, 5 mg intramuscularly to the ewe; ampicillin, 125 mg i.v. to the fetus, and ampicillin, 125 mg into the amniotic cavity. Catheters were kept open by continuous infusion of heparinized saline (5 IU/mL at 1 mL/h). After 4 d of recovery, experiments started with the ewe placed in a stall and having free access to water and food. The experiments were approved by the local ethical committee for animal research.

Experiments. Measurements of transmission pulse oximetry were obtained during a study in which the uteroplacental blood flow was reduced by occluding the common iliac artery. After a 1-h baseline period, the blood flow was gradually reduced, and the onset of metabolic acidosis was studied. Each decreased Sao_2 level was maintained for at least 1 h. Sao_2 samples were obtained for all fetal lambs from 13 to 45% and for five fetal lambs also from 45 to 63%. Fetal arterial blood samples for blood gases and pH (0.2 mL) were taken at 7.5-min intervals, and to reduce total fetal blood loss, for Sao_2 (0.2 mL) at 30-min intervals and after each reduction in blood flow. Samples were taken at the moment that the pulse oximeter displayed stable saturation values (Spo_2). The recovery period started if the pH in the blood sample had fallen to around 7.15 and lasted until baseline levels for pH were reached again. Total blood loss was estimated to be within 10% of the total blood volume. Data for the relation between Sao_2 and the onset of metabolic acidosis and other physiologic parameters are published elsewhere (16). In this study restriction is made to fetal lambs in which transmission sensors were applied both to the muscle and to the skin. At the end of the experiment, the fetus was killed and the fetal instrumentation was verified.

Data analysis. The transmission sensor used in this study was a prototype of the Dura Y-sensor (Nellcor Inc.). All sensors were selected to have identical spectral characteristics. The sensor contains two LED which emit peak wavelengths of 660 nm (red light) and 890 nm (infrared light), a photodiode, and a shielded wire to reduce noise. The red LED has almost 0% secondary emission (see below). The transmission sensors were connected to prototype pulse oximeters (Nellcor Inc.), which are developed for measurements of small pulses. We placed the sensor in a stainless steel support to reduce motion effects. The ECG signal was filtered and passed to the oximeters and was used to cardiosynchronize the red and infrared signals (C-Lock; Nellcor Inc.). In this study the quality scale of the pulse oximeter was used. The signal quality is defined by a scale of 0 to 100%. The calculated value is based on various factors such as pulse amplitude, synchrony of red and infrared wave form and synchrony with the fetal ECG. Spo_2 values were only accepted if the quality of the signal was more than 50%. The failure rate (= time no Spo_2 display/total recording time) was calculated. The fetal blood samples were analyzed within 5 min to obtain the Sao_2 (Instrumentation Laboratories IL482, Lexington, MA), pH and blood gases (Instrumentation Laboratories IL1312). The Sao_2 values were corrected for fetal sheep blood (17). The results of pH and blood gases were corrected to 39°C.

Statistics. The pulse oximeter was provided with a calibration based on measurements with a reflectance sensor in healthy adults (Sao_2 range 50–100%) and fetal sheep (Sao_2 range 10–50%). This calibration might not be optimal for transmission pulse oximetry. We therefore estimated a calibration line with a 95% prediction interval (linear regression least square) for the skinfold measurements in the present experiments. This calibration line was also used for the muscle measurements.

For comparison of two systems measuring the same quantity, with an unknown true value, calculation of the bias and precision is proposed as a measure for the accuracy (18). The bias is defined as the mean difference between the measurements by the two systems and the precision as the SD of the differences. In our measurements the sample Sao_2 value is regarded as the "gold standard" or true value. The SD_{res} (also called SE of estimate) is therefore a good estimation of the random error of the pulse oximeter. The precision will be equal to the SD_{res} if the bias is zero.

From all paired measurements, the mean difference between Spo_2 and sample Sao_2, the precision and the Pearson correlation coefficient were calculated. Linear regression analysis (least squares method) was used to calculate the calibration line and the SD_{res}. Calculations were performed for the transmission sensor around the muscle and the skinfold separately. The regression analysis was also performed for all fetal lambs separately. Significance was held at a p value <0.05.

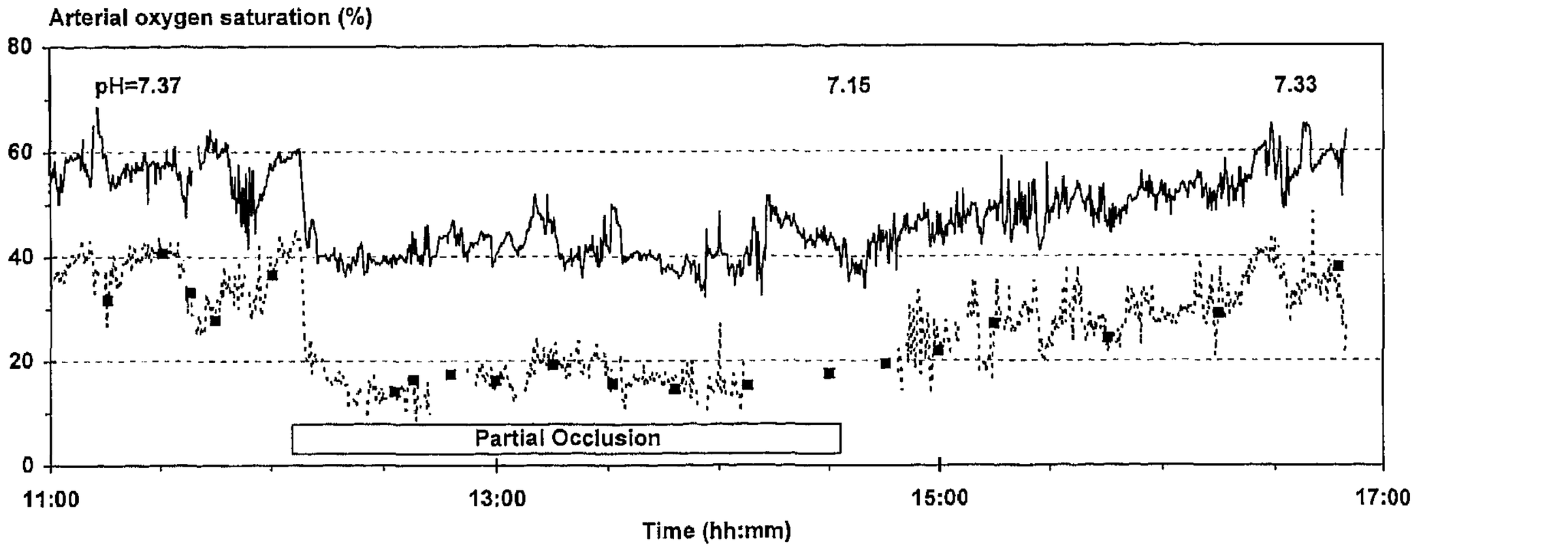

Figure 1. Experiment with period of partial occlusion of the maternal blood flow. Upper Spo_2 tracing of the transmission pulse oximetry sensor around a forelimb muscle (*bold line*), lower Spo_2 tracing of transmission pulse oximetry sensor around double layer of skin (*broken line*), and Sao_2 samples (■). pH values during the experiment are given above the tracing.

RESULTS

In the baseline period, values for Sao_2 ranged from 29 to 45% with corresponding Po_2 values of 1.9–2.4 kPa in two fetal lambs. In five fetal lambs baseline Sao_2 values ranged from 50 to 63% with corresponding Po_2 values of 2.5–2.9 kPa. All animals started with a pH $\geq$ 7.36 in the baseline period.

Fig. 1 illustrates an example of an experiment with partial occlusion of the maternal blood flow (marked period), 4 d after the operation at 131 d of gestation. Blood sample Sao_2 values were measured intermittently, and two transmission sensors measured the Spo_2 continuously. The muscle sensor yielded higher Spo_2 values than those of the skin sensors. No Spo_2 display was obtained around the lowest point of pH for the skin sensor. Both tracings showed considerable fluctuations which often did not coincide. The fluctuations were more pronounced in the recovery period.

For the transmission sensor around the skinfold, 101 simultaneous measurements of Sao_2 and Spo_2 were made over a total Sao_2 range of 14 to 63% (Fig. 2). The precision and the SD_{res} were 5.0%, the Pearson correlation coefficient was 0.93. For the transmission sensor around the muscle of the forelimb, 206 Spo_2 and Sao_2 measurements were made (Fig. 2). All forelimb Spo_2 values were above the line of identity in the Sao_2 range 13–63%. The bias was 19.5% and the precision was 5.9%. The calibration line gave the equation: $Spo_2 = 0.92 \cdot Sao_2 + 21.90$ (SD_{res} = 5.8%, Pearson r = 0.89). Only 7% of all measurements with the transmission sensor around the muscle fell within the 95% confidence interval of the skinfold measurements (Fig. 2).

Individual calibration lines differed substantially between animals (see example in Fig. 3). The SD_{res} for individual calibration varied between 1.9 and 5.7% with a median value of 3.5% for the muscle and between 1.8 and 3.7% with a median value of 3.0% for the skinfold.

The total recording time per experiment ranged between 250 and 465 min. The main failure rate for the transmission sensor around the forelimb muscle was 5% (range 1–10%) regardless of baseline, hypoxemia, or recovery period. For the transmission sensor around the skinfold the mean failure rate was 37% (range 16–63%). Failure rate differed for the baseline, hypoxemia, and recovery period. During the hypoxemia period the amplitude of the plethysmographic waveforms started to decrease, and the pulse oximeter stopped displaying Spo_2 values. The mean value for pH at that moment was 7.31 (range 7.20–7.35). During the recovery period the pulse oximeter started again to display Spo_2 values at a pH value of 7.23 (range 7.20–7.34).

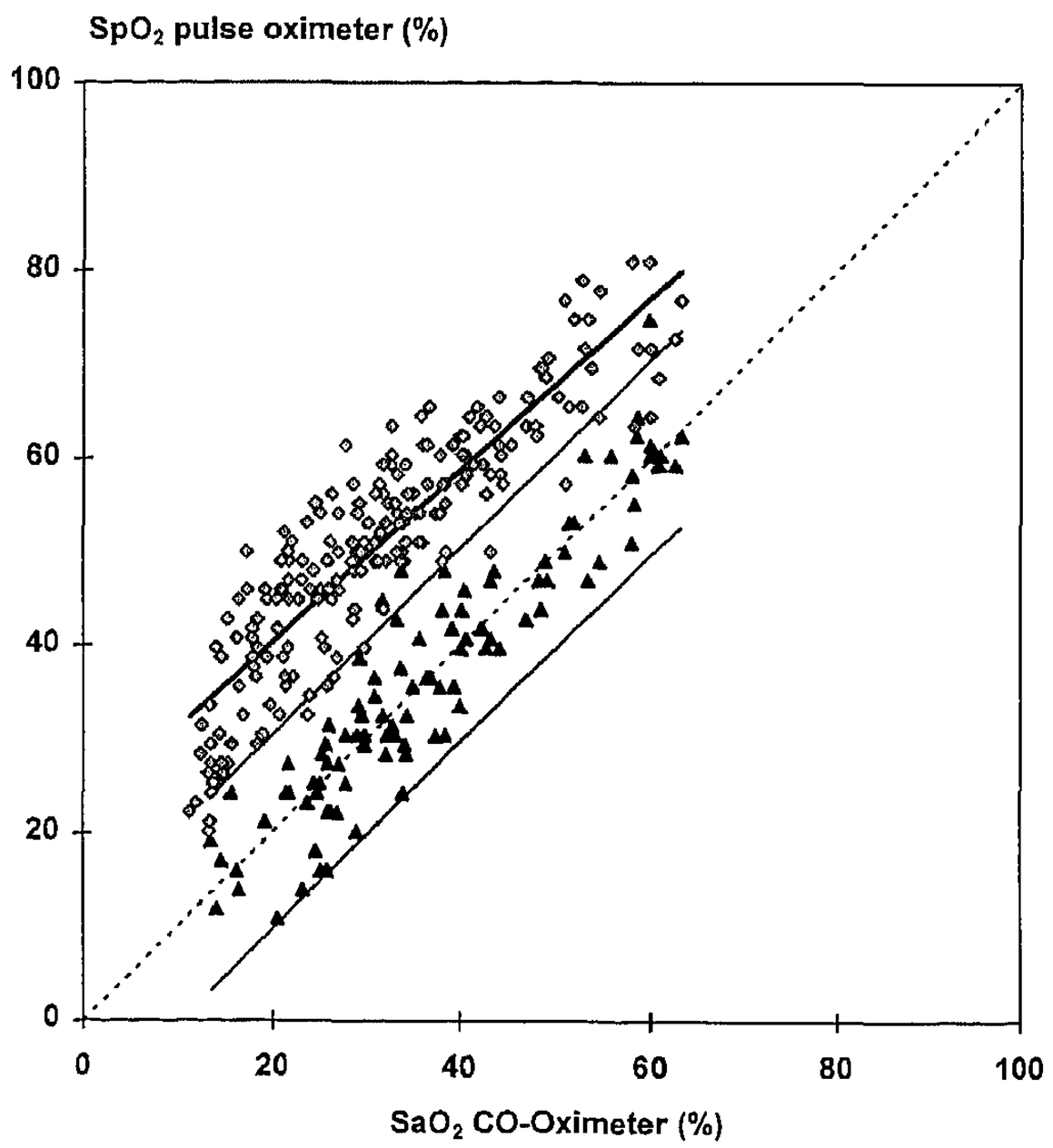

Figure 2. Sao_2 measured by the multiwavelength oximeter against the Spo_2 values obtained with the pulse oximeters; ▲, transmission pulse oximetry around skinfold with 95% prediction interval; ◈, transmission pulse oximetry sensor around forelimb muscle; *bold line* is regression line for transmission pulse oximetry around forelimb muscle: $Spo_2 = 0.92 \cdot Sao_2 + 21.90$. *Broken line* is line of identity.

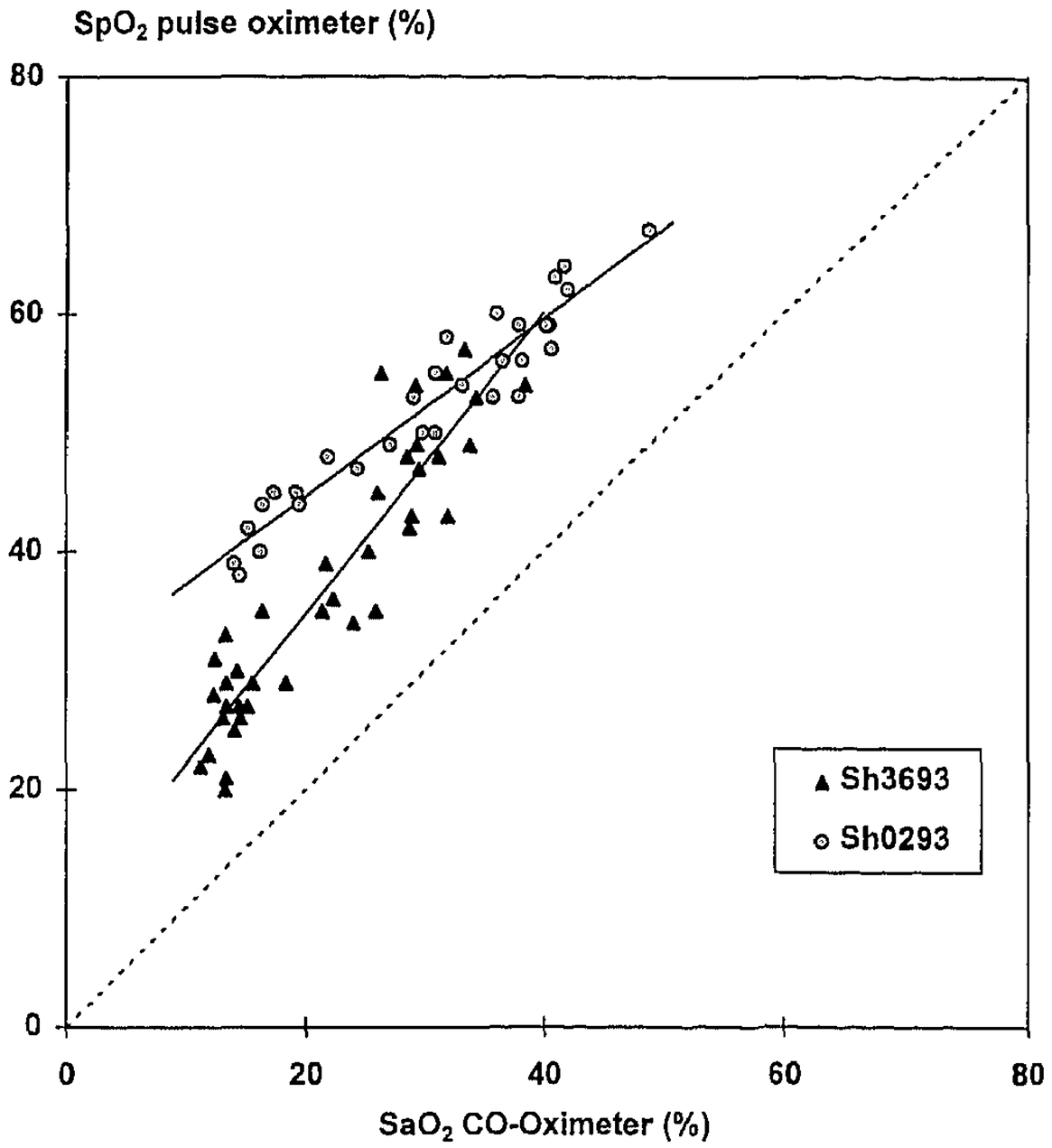

Figure 3. Sao_2 measured by the multiwavelength oximeter against the Spo_2 values obtained with the pulse oximeter, for the transmission pulse oximetry sensor around a forelimb muscle in two fetal lambs. The figure shows the difference between individual calibration lines. *Broken line* is line of identity.

DISCUSSION

Continuous and accurate assessment of arterial oxygenation is important in clinical management of critically ill or anesthetized patients and could be useful in monitoring the fetus during labor. Although experimental fetal monitoring is mostly done with reflectance pulse oximetry (6, 7), transmission pulse oximetry might be a possible alternative (19). Commercial transmission pulse oximeters have shown to be devices with a reported precision within 3%, for Sao_2 values between 70 and 100% (1–5). Below an Sao_2 of 70% some accuracy studies have been performed in humans with desaturation levels as low as 40 to 70% (20, 21). Various pulse oximetry systems were tested, and all proved to be less accurate at low Sao_2 levels (20, 21). However, in these studies low saturation levels were provoked for only a very brief period. Low levels of saturation were not stable at the moment of measurement, which may have resulted in a less reliable estimation of the accuracy. Becaue controlled studies at these low levels are unethical to perform in humans, animal models provide adequate alternatives. Moreover, light absorption characteristics for Hb in the spectral range used have shown to be similar for different mammals (13, 14) and do not affect the results, nor does fetal Hb (22). We therefore investigated the performance of transmission pulse oximetry in the fetal lamb.

Because none of the commercial oximeters is constructed for these low Sao_2 levels, we used a prototype pulse oximeter. Commercial pulse oximeters use a calibration line based on measurements in human volunteers with Sao_2 values above 70%, which cannot be extrapolated toward lower Sao_2 values. Furthermore, commercial pulse oximeters sometimes stop displaying Spo_2 values below 50%. The pulse oximeter, used in this study, is constructed as a possible monitoring device for the fetus during labor and has the advantage that it is more sensitive to the small fetal pulses. The incorporated calibration line in the pulse oximeter is based on fetal sheep scalp measurements (Sao_2 range 10–50%) and measurements in human adults (Sao_2 range 50–100%) with reflectance pulse oximetry. Although the pulse oximeter Spo_2 readings based on this incorporated calibration did not differ much for the skinfold measurements (the bias would have been −0.6% for skinfold measurements), we calibrated the pulse oximeter for transmission pulse oximetry using the skinfold measurements of the present experiment. This small difference between the calibration line for the skin measurements and the incorporated calibration line for reflectance pulse oximetry is regarded as coincidental, but theoretical models have shown that if the separation distances are properly scaled, the calibration lines measured in the two modes can be almost the same (23). The prototype Y-sensors differed from the commercial Dura Y-sensors (Nellcor Inc.) and Oxibands (Nellcor Inc.) with respect to the spectral characteristics. All the prototype Y-sensors were constructed with identical red and infrared LED. The emission from the red LED showed a single peak at 660 nm and did not show an additional small emission peak of a second wavelength. The presence of this so called "secondary emission" does not influence the accuracy at high Sao_2 values, but may be of importance at low Sao_2 values (15). In commercial sensors this secondary emission is often present (15).

For the sensor around the skinfold, Spo_2 readings reflected the blood sample Sao_2 values fairly well in all recordings, with a precision of 5.0%. For the forelimb muscle, we found a completely different calibration line between Sao_2 values and Spo_2 readings, with an average bias of 19.5%. The random error for the muscle sensor was slightly higher than for the skin sensor. The effect of the stepwise occlusion could be clearly observed in all recordings. However, alongside this period of desaturation, fluctuations in the Spo_2 readings were also present (see Fig. 1). These fluctuations in Spo_2 may be the result of physiologic saturation fluctuations or technical artifacts. The distinction between those two possibilities is difficult and therefore measurements were only taken during a stable period of pulse oximetry Spo_2 reading. Baseline Sao_2 values showed a wide range. However, none of the fetal lambs were hypoxic in the sense that anaerobic metabolism was needed. No differences in signal loss were observed between the animals with high Sao_2 baseline levels compared with animals with low Sao_2 baseline levels.

To compare our results with other animal studies, the random error of the pulse oximeter is a valid measure. The bias as a measure for the underestimation or overestimation of the pulse oximeter is less suitable for a comparison, because this calculation is dependent upon the calibration line inserted into the pulse oximeter. A random error of around 5% is comparable with the results of Sendak *et al.* (13) in dogs. They placed the sensor around the dog's tongue and found a precision of 4.2% between 22 and 100% Sao_2, but the precision was only half as good between 8% and 22% Sao_2 (13). Other experimental studies in dogs (12) and rabbits (14) reported even

worse results for the accuracy of transmission pulse oximetry at Sao_2 levels below 70%.

To our knowledge, this is the first time that simultaneous measurements, at two sites in an *in vivo* model, resulted in a difference in calibration lines. Both the skinfold in the neck and the forelimb muscle are provided with preductal blood (above the ductus arteriosus). Several explanations for the difference between muscle and skinfold calibration lines can be raised. First, malpositioning of the sensor can cause unreliable Spo_2 pulse oximetry readings. A falsely low or high Spo_2 reading was shown by Barker *et al.* (24) to be due to shunting of light from the LED directly toward the photodiode. In this study we verified fetal instrumentation after the experiments. All sensors made proper contact with the tissue. For the transmission pulse oximetry sensor around the muscle, the sensor was completely fixed by the recovered muscle tissue. It is therefore unlikely that this shunting of light can explain our results. Second, the tissue of skin and muscle is very different with respect to the amount of myoglobin. Myoglobin is a chromophore and has extinction coefficients in the same spectral range as Hb, which may result in differences of absorption of red and infrared light. It is expected that only oxymyoglobin will be present in the measured Sao_2 range, because myoglobin unloads oxygen at a very low Po_2 (25). The pulse oximeter uses only the red to infrared pulsatile changes of the blood volume for the estimation of the Sao_2, and it can therefore hardly be expected that myoglobin would also show cardiosynchronous changes in absorption. Finally, there is the difference in blood content. Muscle tissue contains much more blood than skin tissue. Theoretical models which incorporated the effects of multiple scattering and absorption (23) predicted that, due to increased blood volume, the pulse oximeter overestimates the Sao_2 below 70%, which agrees with our results. Unpreventable differences in the amount of tissue between LED and photodiode between animals, and therefore in blood content, may be an explanation for differences in calibration lines between animals. Differences in myoglobin concentration (26) and tissue structure may also have an influence on the scatter and absorption characteristics, which influence the accuracy of transmission pulse oximetry pulse oximetry at low Sao_2 values. These scatter and absorption characteristics will probably change under hypoxic conditions, as blood flow to the skin and carcass decreases (27).

The basic principles of transmission and reflectance pulse oximetry are the same. Reflectance pulse oximetry is even more sensitive to differences in optical properties of the tissue, and therefore changes in *in vivo* calibration can also be expected for this application (23). *In vitro* models have been developed (28) to study the accuracy of pulse oximetry, but these models often use homogeneous media which are simplifications of the heterogeneous medium of skin and underlying tissue structures.

Clinicians should therefore be aware that applying sensors around different tissue structures; *e.g.* foot, hand, achilles tendon, nose, or ear may reveal differences in calibration below an Sao_2 of 70%. Although in neonatal practice pulse oximeters are mostly used to monitor the Spo_2 trend above 70% saturation, systematic differences may be hazardous for fetal monitoring because fetal saturation values are predominantly below 70%. In fetal lamb hypoxemia studies, the application of the transmission pulse oximetry sensor around the skinfold was not suitable because, during prolonged hypoxia, the oximeter failed to display Spo_2 values due to a diminished skin blood flow. For the sensor around the forelimb muscle, continuous Spo_2 recordings were obtained, also during prolonged hypoxemia. The accuracy of the general calibration line was moderate but could be improved substantially by taking individual calibration lines which has a disadvantage that sufficient blood samples are needed. For human fetal monitoring, however, this is not possible and a transmission sensor around a muscle is not a realistic alternative.

In conclusion, transmission pulse oximetry is relatively accurate in fetal lambs below an Sao_2 of 70%. At these low levels of Sao_2, pulse oximeters may need to be constructed with different calibration lines for various application positions on the body. For fetal application this is not possible because arterial blood samples cannot be obtained. More studies are therefore needed for the development of accurate pulse oximetry systems for a low Sao_2 range.

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