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The measurement of accurate fetal hemoglobin and related oxygen saturation by the hemoximeter

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Abstract

Background—The purposes of this study were to examine the accuracy of fetal hemoglobin (HbF) as quickly measured by the hemoximeter, verified by the high-performance liquid chromatography method, and to examine related oxygen saturation (SO₂) measurements in neonates.

Methods—Thirty-nine neonates with gestational ages ranging from 25 to 38 weeks were investigated (*n*=280 blood samples). Twenty younger premature neonates had blood transfusions (*n*=188 blood samples, 72 before and 116 after transfusions), and 19 older neonates did not.

Results—The bias of the hemoximeter was 23% (±9.1) against the HPLC; 25% (±7.9) before, and 19% (±8.6) after blood transfusions (all *P* < 0.001), for HbF measurements. A regression line (HbFt by the HPLC = 8.46 + 0.7 × HbF by the hemoximeter) has been provided for the prediction. Oxyhemoglobin dissociation curves with the status of (before and after) blood transfusions were presented. In relation to oxygen tension values of 50–75 mm Hg, in addition to the right-shifted oxyhemoglobin dissociation curves, pulse oximeter ranged from 95 to 98% before the transfusions, but decreased to 94 to 96% after the blood transfusions.

Conclusions—Accurate HbF and related oxygen saturation measurements need to be determined, especially for premature neonates, to minimize the risk of oxygen toxicity.

Keywords

Hemoglobin; Transfusion; Fetal hemoglobin; Acetylated fetal hemoglobin; Hb oxygen saturation

1. Introduction

Fetal hemoglobin (HbF) differs from adult hemoglobin (HbA) in that it has 2 γ chains in place of the 2 α chains, and has a higher oxygen (O₂) affinity thus presenting a left-shifted oxyhemoglobin (HbO₂) dissociation curve in neonates [1,2]. When HbF levels were not adjusted, carbon-monoxide hemoglobin (HbCO) and oxygen saturation (SO₂) measurements were arbitrarily increased for 6% in neonates [1–4]. The differences (bias) between the blood SO₂ and pulse oximeter SO₂ (SpO₂) were reported to increase as the SO₂ decreased [5–7], however, HbF levels did not change the difference between the blood and pulse oximeter

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SO₂ [5,6]. To date, however, limited data is available regarding the changes of HbF levels of neonates on the accurate measurements of HbO₂ and SO₂.

Although the hemoximeter method is available for the quick estimate of HbF levels in clinical settings; a high-performance liquid chromatography method remains as the most sensitive, accurate, and practical method to determine HbF and HbF variations [8–11]. Acetylated HbF (HbF1) is a variation of HbF, a posttranslational modification of HbF by acetylation of the N-terminus of γ globin chains [12,13]. Its O₂ carrying capacity was reported as dysfunctional, irresponsive to 2,3 diphosphoglycerate (2,3 DPG) binding to facilitate O₂ release at tissue level [13,14]. Therefore, accurate HbF measurement is essential to assess adequate oxygenation and to prevent O₂ related complications in these neonates [7,15].

Blood transfusion using HbA could improve a neonate's tissue oxygenation [16,17]; however, when the blood was transfused in larger volume in a short period, a right-shifted HbO₂ dissociation curve may cause O₂ toxicity [18] and add cardiac load [19]. Thus, HbA blood should be transfused slowly and SO₂ measurements should be monitored closely following blood transfusions in neonates [18,19]. For functional SO₂ measurements in relation to the HbF changes in neonates, 2 previous small studies ($n=10$, and 11) have reported the right-shifting HbO₂ dissociation curves following blood transfusions using P₅₀ measurements [17, 20]. Widespread clinical pulse oximeter (SpO₂) readings had been reported in relation to the PaO₂ values without providing a precise HbO₂ dissociation curve for neonates [21] in relation to the clinical PaO₂ ranges of 50–75 mm Hg [22], related SO₂ measurements need to be established for neonates, accounting for the effects of HbF levels. The purposes of this study were, therefore, to examine: 1) the accuracy of HbF measurements using the hemoximeter against the HPLC method; and, 2) the changes HbO₂ dissociation curves and SO₂ measurements, following blood transfusions.

2. Methods

2.1. Setting

This study is part of a larger clinical study in 2 neonatal intensive care units (NICUs) [23]. The appropriate institutional human subjects review boards approved the study protocols. Informed consents were obtained from the parents and guardians of newborn subjects prior to or immediately following birth. For this study, all neonates had successful insertions of umbilical arterial catheters (UAC) and/or umbilical venous catheters (UVC) to monitor SaO₂ or SvO₂.

2.2. Sample

Immediately after birth, neonates who were diagnosed with respiratory distress syndrome requiring mechanical ventilation were randomly selected into the study from a possible pool of 100 consecutive newborn infants. Those with major congenital defects (cardiac, brain and neurological, or gastro-intestinal defects) were excluded, as interpretation of accurate SaO₂ and SvO₂, would be problematic in these cases. Neonates who had life-threatening persistent pulmonary hypertension requiring inhaled nitric oxide or extra-corporeal membrane oxygenation were also excluded for feasibility concerns. The sample included 39 neonates, and provided 280 blood samples (ranging from 1 to 19, at least 1 sample per day). Gestational ages of these newborns ranged from 25 to 38 weeks, and birth weights from 665 to 3696 g. Neonates with lower birth weights were not included because of their small size limiting the insertion of the 4F monitoring catheter and amount of blood that could be drawn.

2.3. Instruments

2.3.1. Hemoximeter—HbF and SO₂ measurements [including total Hb (tHb), HbO₂, SO₂, HbCO, and met-Hb (MetHb)] were analyzed by using the hemoximeter model OSM3

(Radiometer Corp, Cleveland, OH), using 6-wavelength fiber optic reflectance oximetry (535, 560, 577, 622, 636, and 670 nm). The accuracy of this co-oximeter, as reported by the manufacturer, is a test–retest variability of <0.1% for normal Hb level, and –0.2% to +0.4% for extreme anemia and polycythemia (tHb ranges: 3.2 to 28 g/dl). The instrument allowed in-vitro measurements of HbF concentrations through determination of P₅₀ on the HbO₂ dissociation curve based on a linear assumption of maximum oxygenation status by fully-oxygenating the sample [24]. To follow the recommended guidelines from a consensus meeting for SO₂ measurements [25], the cap for the restrictions of 100% maximum for HbF, SO₂ and HbO₂ measurements was removed, so that the test results exceeding 100% could be reported by the equipment. Validity was assured by 0-point calibration using the manufacturer's rinse solution before and after each test. Quality control procedures included the reference method every 8 h, cleansing the internals of tubing with appropriate solutions every week, and changing maintenance tubing and tHb calibration every quarter, to assure test accuracy.

2.3.2. HPLC—Analyses of Hb and its variants were performed by using a Varian cation-exchange HPLC system (Varian Instruments, Walnut Creek, CA; Varian 5500 HPLC interfaced with a Vista 654 Data system, a Waters Model 440 detector and a Perkin Elmer ISS 100 auto-sampler). A 200S × 4.6 mm Poly CAT A column packed with 5µm particle, porous silica coated with polyaspartic acid was obtained from Poly LC Inc. (Columbia, MD). The sample preparation, mobile phase composition, and chromatographic conditions have been described before [8,9]. Briefly, hemolysates were prepared by mixing the washed packed red cells with 2 volumes of water for 30 s. After lysis, 50µl of hemolysate were added to 1 ml of mobile phase A. The mixture was then centrifuged at 3000 ×g for 5 min and 10µl of supernate were injected onto the column. The chromatographic separation of all Hb was achieved by gradient elution with 2 mobile phases at 2 different pH (6.57 and 6.87) levels with flow rate set at 0.6 ml/min. The peak areas were measured at 436 nm. This method was developed and optimized for the high resolution of more than 45 commonly encountered Hb variants (including HbF, HbA₂, HbF₁, HbS, HbC etc. in addition to HbA) within 12 min [4].

Clinical monitor readings included pulse oximeter readings, respiratory rate and heart rate readings, and incubator temperature and skin temperature readings. SpO₂ readings were recorded by using a pulse oximeter (Nellcor NPB 290, Tyco HealthCare, Mansfield, MA). This instrument was capable of measuring the percentage of peripheral SO₂, detected transcutaneously by a probe positioned on either side of a pulsating arterial bed around the neonate's foot. The transmittance sensor was configured so that the light-emitting diodes transmit infrared and red light through the pulsating vascular bed to a photo-detector positioned on the opposite site. For reading consistency purposes, the sensors for pulse oximeter were all placed on post-ductal sites. The pulse oximeter has shown moderate to good correlations ($r=0.5, 0.88$) with accounting for the HbF effects [3,26]. Inter-rater agreement on data coding reached 100% agreement between the 2 raters.

2.4. Procedures

Blood was drawn through the UAC or UVC from the day of admission to 5 days old, coordinated to occur simultaneously about every 8 h with routine blood gas tests when neonates were resting quietly to obtain stable measurements. For the hemoximeter analyses, an extra 0.1 ml blood was split into 2 syringes for the HbF test and the SO₂ tests. HbF determination required oxygenating blood samples with 100% O₂ and twirling the syringe between the hands for 90 s to yield fully oxygenated samples. The oxygenation status was confirmed by SO₂ readings close to 100%. HbF was then determined by using a linear assumption model. Since SO₂ using fully oxygenated blood can only reach a maximum of 100% (with 0% HbF), a linear formula programmed in the hemoximeter would yield 106% SO₂ with 100% HbF, and this

program would thus estimate the HbF levels based on this formula [24]. Study personnel completed the training and execution of blood-handling protocol [3].

Once the hemoximeter analyses were completed, the residual blood was stored in a refrigerator, and the samples were transported in an icebox and sent for HPLC analyses within a 2-day period during weekdays daytime hours. To obtain the most accurate HbF measurements by the hemoximeter and the corresponding HPLC method, the daily samples with the highest HbF levels determined by the hemoximeter were sent for HPLC analyses. Medical records were prospectively reviewed to obtain a subject's demographic data, medical history, and routine laboratory tests and monitoring parameters.

2.5. Data analysis

Data were analyzed by using the Statistical Packages for Social Sciences (SPSS ver. 13.0, Chicago, IL). The technique of Bland and Altman [27] was used to calculate bias, precision, and the limits of agreement. The bias was defined as the mean difference (paired *t* test) between the hemoximeter and the HPLC measurements for HbF levels, and the precision as the SE of the mean difference. The limit of agreement was defined as ± 2 SD for the differences between 2 measurements. In addition, multivariate regression analysis was performed to predict HbF levels for the hemoximeter using the data from the HPLC. Thereafter, HbO₂ dissociations were examined by using multiple regression (R) curve-fitting analysis on Sigmoid (S) curve, for PO₂ values and all SO₂ measurements (HbO₂, SO₂, and SpO₂).

3. Results

Table 1 presents the descriptive statistics for the demographic data of this study. There were 20 girls and 19 boys for the 39 subjects; while 19 subjects did not have any blood transfusions, 20 subjects had blood transfusions. The racial/ethnic compositions of the study sample included 15 African Americans, 2 Asian Americans, 4 Caucasians and 18 Hispanics. Those who had blood transfusions had lower gestational ages and birth weights, and had longer hospital stays compared to those who did not have blood transfusions (all $P < 0.01$). The volume of blood transfusion for these neonates ranged from 3 to 5 ml kg/h, lasting 2–3 h.

Table 2 presents the descriptive statistics for the HbF analyses using the HPLC and the hemoximeter methods for 72 blood samples prior to blood transfusions and 116 blood samples following blood transfusions (presented with only the data of neonates who had blood transfusions for comparisons). The blood samples were drawn on an average at 22 h after birth, prior to blood transfusions, and 76 h after birth, following blood transfusions. Additional analyses using the hemoximeter analysis for SO₂ measurements (including tHb, HbO₂, SO₂, HbCO, and MetHb), as well as the simultaneous recorded clinical monitor readings and blood gas parameters are presented. Before blood transfusions, there were 5 samples with elevated HbC (1.7–2.8%) from 2 neonates (both African Americans, 26 and 31 weeks gestation each), and 3 samples with elevated HbA₂ from another neonate (African American, 38 weeks gestation). After blood transfusions, 98 samples (84%) had elevated HbA₂ levels, and additional 2 subjects (5 samples) showed increased HbC levels. Following the blood transfusions, HbF levels decreased (HPLC: $94\% \pm 3.0$ before, and $64\% \pm 11.3$ after transfusions; hemoximeter: $119\% \pm 9$ before, and $82\% \pm 16.4$ after transfusions), and HbA levels increased (HPLC: $6.5\% \pm 3.1$ before, and $35\% \pm 11.1$ after transfusions) (all $P < 0.001$). In addition, following the blood transfusions, bicarbonate levels increased ($P < 0.05$) with lower PO₂ in the blood, and SpO₂ decreased ($P < 0.01$); compared to those samples prior to the blood transfusions.

4. Accurate HbF measurements

For the summary statistics between the HPLC and the hemoximeter methods ($n=280$ blood samples), the bias for the hemoximeter was 23% (± 9.05 , higher for the hemoximeter) ($25.3\% \pm 7.85$ and $18.7\% \pm 8.62$, before and after the transfusions). The precision was 0.54 (0.64 and 0.80, before and after the transfusions). The correlation for the HbF measurements using the 2 methods was 0.93 (0.56 and 0.87 for the data before and after the transfusions, all $P < 0.001$). The limit of agreement ($+2SD$) was 18.1%, and the disagreement (outside or exceeding the limit of $\pm 2SD$) was 0%.

Using the multivariate regression approach, HbF levels were predicted for the hemoximeter measurements, against the HPLC measurements ($n=280$ blood samples). Fig. 1 presents the scatter plots and a regression line comparing HbF measurements using the 2 methods ($HbF_t = 8.46 + 0.7 \times HbF$ by hemoximeter, $R^2 = 0.87$, all $P < 0.001$). Using this formula, if the HbF levels determined by the hemoximeter method is 120%, the HbF_t level predicted for the HPLC method would be 92.5% (rounded to 93%); and if the HbF level by the hemoximeter is 90%, the HbF_t predicted would be 72%.

5. HbO₂ dissociation curves

Fig. 2 presents the fitted S-curves, before and after the blood transfusions, using the arterial blood samples for those who had blood transfusions ($n = 188$ blood samples). For the ease of visualization, the ranges of PO₂ values were focused close to the critical ranges of 50 to 75 mm Hg. In relation to the critical ranges of 50 to 75 mm Hg PaO₂, arterial HbO₂ ranged from 91 to 94% before transfusions ($R^2 = 0.45$, $P < 0.001$, $n = 72$), and 90 to 93.5% after transfusions ($R^2 = 0.65$, $P = 0.001$, $n = 116$). SaO₂ ranged from 94 to 97% before transfusions ($R^2 = 0.38$, $P < 0.001$, $n = 72$), and 93.5 to 97% after transfusions ($R^2 = 0.63$, $P < 0.001$, $n = 116$). And, SpO₂ ranged from 95 to 98% before transfusions ($R^2 = 0.43$, $P < 0.001$, $n = 72$), and 94 to 96% after transfusions ($R^2 = 0.23$, $P < 0.001$, $n = 116$).

6. Discussion

To continue a previous report on predicting the HbF levels of HPLC method using the hemoximeter method [28], we reported a linear regression model with a much better correlation coefficient with blood transfusions for neonates. This linear regression line might be useful in clinical settings for the measurements of the hemoximeter, to predict the most accurate HbF levels. The HbF levels $>100\%$ determined by the hemoximeter were actually biased and represented inaccurate measurements. Thus, accurate HbF measurements using the HPLC method are needed for neonates in clinical settings [9,10].

Wimberly et al. examined HbF effects on SO₂ measurements using 11 cord blood samples of healthy term neonates [1,2]. This study included more blood samples and data points for HbF and related SO₂ measurements to compare the hemoximeter readings against the HPLC in neonates. Following the blood transfusions, HbO₂ dissociation curves were right-shifted in these neonates [17,20], and we substantiated these right-shifted S-curves with decreased blood and clinical oximeter oxygen saturation readings in relation to the same ranges of PaO₂ values. In relation to the critical PaO₂ value of 50 mm Hg (for the critical value for hypoxemia), following the blood transfusions, arterial HbO₂ was 1% lower (91% to 90%), SaO₂ was 0.5% lower (94 to 93.5%), and SpO₂ was 1% lower (95% to 94%), when compared to the measurements prior to the blood transfusions. In addition, following the blood transfusions, PO₂ was lower in the blood with increased bicarbonate levels, and pulse oximetry was lower compared to those prior to the blood transfusions. For these premature neonates who had blood transfusions, there was a tendency of increased heart rate and respiratory rate following the transfusions (but not statistically significant). Thus, HbF levels and oxygenation status of these

premature neonates need to be monitored closely following the blood transfusions, to prevent potential oxygen toxicity [18–20].

Neonates who need O₂ supplementation are prone to develop oxygenation complications with HbF releasing less O₂ (than HbA) to the tissue. HbF₁ (acetylated HbF) is a variation of HbF; and, it is non-functional to release O₂. Thus, the presence of HbF₁ needs to be taken into considerations when assessing oxygenation status. Future studies are needed to examine the changes of HbF and HbF₁ and their effects on the SO₂ measurements in neonates, particularly for those who had hypoxia and had the history of maternal chronic diseases. Future studies also need to integrate the methods used in this and other studies, including P₅₀ measurements, to assess HbF levels and related oxygen saturation measurements more accurately for premature neonates, to minimize the risks of oxygen toxicity with blood transfusions.

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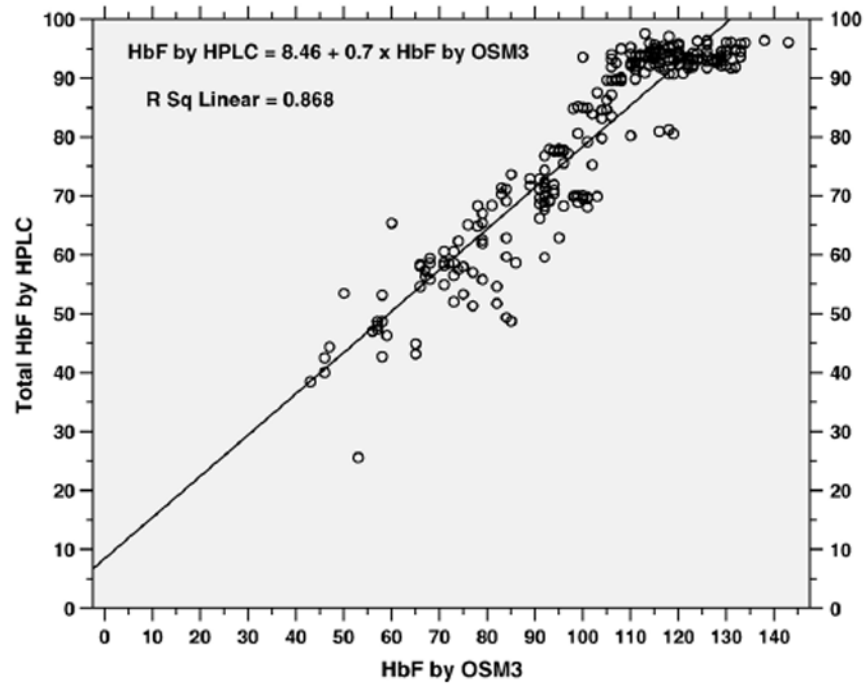


Fig 1. Scatter plots of HbF measured by OSM3 hemoximeter (X-axis) and HbF (%) measured by HPLC (Y-axis) with a regression line ($n = 280$ blood samples).

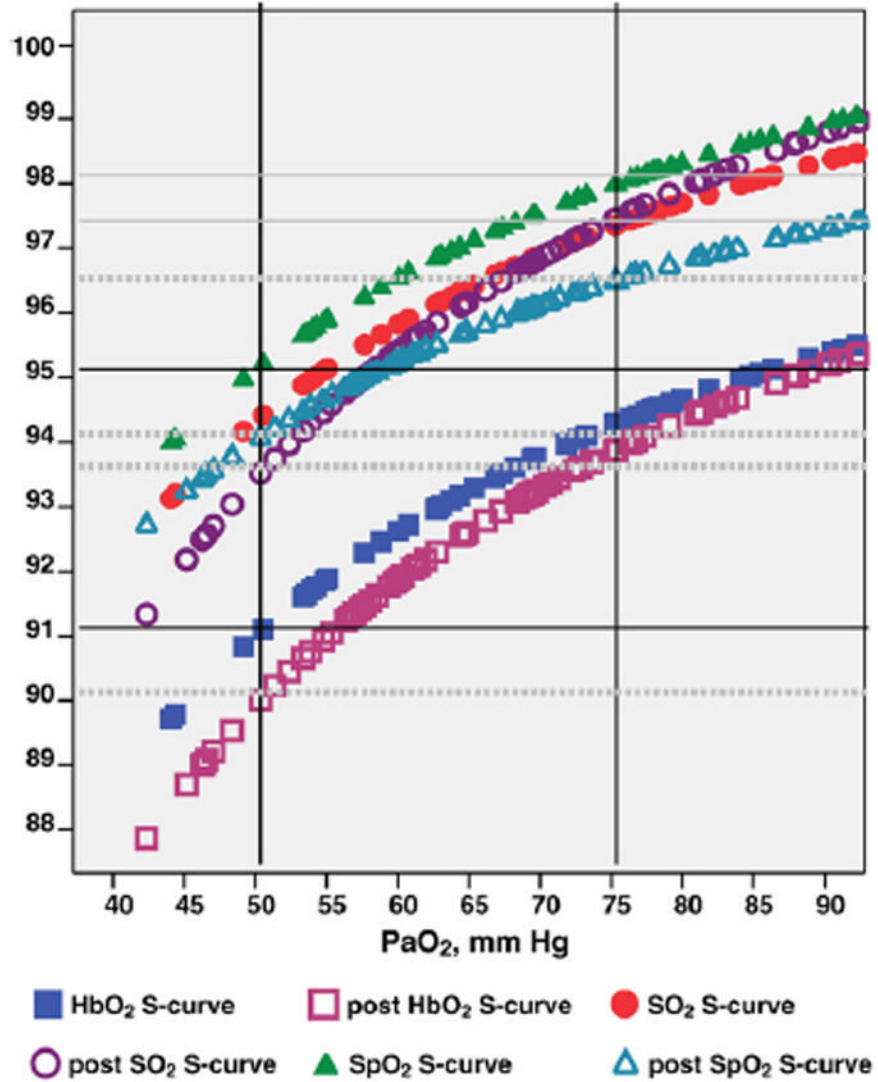


Fig 2.

Fitted Sigmoid curves for arterial HbO₂, SaO₂, and SpO₂ before ($n = 72$ blood samples) and after ($n = 116$ blood samples) blood transfusions of HbA (solid markings = before transfusions, hollow markings = after transfusion); X-axis: arterial blood gas PO₂ (mm Hg); Y-axis: arterial oxygen saturation measurements (%). Note: HbO₂ = oxyhemoglobin, SO₂ = arterial oxygen saturation, SpO₂ = oxygen saturation by pulse oximetry, PaO₂ = arterial oxygen tension.

Table 1

Descriptive statistics for demographic data by groups of neonates who had transfusions of adult blood within the first 5 days after birth ($n = 39$ subjects)

Mean \pm SD (ranges)	No transfusion ($n = 19$)	Transfusion ($n = 20$)
Gestation weeks, at birth **	32.7 \pm 2.72 (28–38)	29.5 \pm 3.03 (25–37)
Gestation weeks mother admitted **	32.2 \pm 2.72 (28–38)	28.4 \pm 2.93 (24–32)
Birth weight, g ***	1798 \pm 672 (992–3695)	1178 \pm 347 (665–1843)
NICU days **	26 \pm 18.5 (3–79)	65 \pm 38.2 (8–139)
Hospital days **	33 \pm 27.0 (8–120)	67 \pm 36.6 (8–139)
Gender (boy/girl)	8/11	11/9
Race/ethnicity		
Hispanics	8	10
Black	6	9
White	3	1
Asian	2	0

**
 $P < 0.01$

 $P < 0.001$

NICU = Neonatal Intensive Care Unit

Table 2

Descriptive statistics before and after the blood transfusions (n=188 blood samples)

Mean±SD	No transfusions (n=72)	After transfusions (n=116)
Hours after birth ***	21.6 ± 17.35	75.6 ± 29.55
HPLC		
HbFt, % ***	93.9 ± 3.02	63.9 ± 11.34
HbF*, % ***	83.3 ± 2.90	56.4 ± 9.97
HbF1, % ***	10.2 ± 2.29	7.54 ± 1.96
HbA, % ***	6.5 ± 3.14	35.4 ± 11.14
HbA2, % ***	0.01 ± 0.07	0.75 ± 0.45
HbC, %	0.18 ± 0.69	0.11 ± 0.38
Hemoximeter		
tHb, g/dl	12.2 ± 2.45	12.6 ± 1.87
HbF, % ***	119 ± 9.02	82.4 ± 16.40
HbO ₂ , %	94.1 ± 3.04	93.4 ± 2.76
SO ₂ , %	97.2 ± 3.05	96.9 ± 2.87
HbCO, % ***	1.8 ± 0.76	2.4 ± 0.63
MetHb, % **	1.3 ± 0.21	1.2 ± 0.23
Clinical monitor		
Pulse oximeter SO ₂ % **	97.6 ± 2.73	96.2 ± 2.79
Pulse rate/min	142 ± 14.67	146 ± 13.84
Respiratory rate/min	36 ± 17.77	43 ± 25.22
Skin temperature °C	36.4 ± 0.32	36.4 ± 0.30
Blood gas		
p ^H	7.34 ± 0.09	7.33 ± 0.08
PO ₂ , mm Hg *	87.9 ± 48.0	77.3 ± 22.7
PCO ₂ , mm Hg	41.8 ± 11.27	44.3 ± 9.37
Bicarbonate, mmol/l *	21.5 ± 2.06	22.3 ± 2.58
Base excess	-3.6 ± 2.30	-3.0 ± 2.90

Note: HbF = fetal hemoglobin. HbF1 = acetylated fetal hemoglobin, HbA = adult hemoglobin, HbA2, adult hemoglobin A2.

* $P < 0.05$

** $P < 0.01$

*** $P < 0.001$.