Ophthalmic Artery Blood Flow in Very-Low-Birth-Weight Preterm Infants

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PURPOSE. To evaluate normal blood flow velocity and Doppler indices of the ophthalmic arteries from birth to hospital discharge of inborn infants at birth weights between 500 and 1500 g and gestational age ≤32 weeks.

METHODS. A longitudinal prospective study with Doppler ultrasound was conducted in both eyes at 24 hours, 7 and 28 days, and hospital discharge for systolic and diastolic velocities, pulsatility, and resistance indices. Retinopathy of prematurity stage 2 or 4, and death were excluded.

RESULTS. The authors studied 46 very-low-birth-weight infants (92 eyes; birth weight, 1215 ± 202 g; gestational age, 30.4 ± 1.5 weeks). Both eyes had similar Doppler findings at birth and at each study interval. Systolic velocity increased significantly from birth to hospital discharge (P = 0.001; right eye, 17.85 ± 5.3 cm/s and 23.18 ± 4.88 cm/s; left eye, 17.78 ± 5.19 cm/s and 23.51 ± 5.63 cm/s), as did diastolic velocity (P = 0.02; right eye, 6.17 ± 1.13 cm/s and 6.76 ± 1.12 cm/s; left eye, 6.34 ± 1.26 cm/s and 6.9 ± 1.53 cm/s). Pulsatility and resistance indices did not change during the entire period.

CONCLUSIONS. There is a typical pattern of ophthalmic artery systolic and diastolic blood flow velocities, and pulsatility and resistance indices during the neonatal period in very-low-birth-weight infants. (Invest Ophthalmol Vis Sci. 2010;51:708–711) DOI:10.1167/iovs.09-4206

Intracranial and retinal blood flow share the same control mechanisms, and both circulations are supplied by branches of the internal carotid artery.1 Peri-intraventricular hemorrhage and retinopathy of prematurity are common diseases in very-low-birth-weight preterm newborns.2,3 Both are vascular-circulatory disorders related to altered blood flow. Peri-intraventricular hemorrhage is an important risk factor for delayed neurodevelopment of very-low-birth-weight infants,2 and retinopathy of prematurity is a prevalent cause of blindness.4

Studies indicate that changes in retinal blood flow are involved in the pathogenesis of retinopathy of prematurity because such changes cause an abnormal growth of vascular vessels of the immature retina.5,6 Examination of the retinal blood flow may also serve as a window for intracranial circulation evaluation. Hence, it is important to establish in a longitudinal study normal ranges for ophthalmic artery blood flow in very-low-birth-weight infants. Data regarding values of normal flow in ophthalmic artery in newborns are scarce, limited to the first week of life, and refer only to term newborns.7,8

The objective of the study was to measure blood flow velocity of the ophthalmic artery and its related indices in very-low-birth-weight preterm infants during their stays in the neonatal intensive care unit.

METHODS

A prospective cohort study included newborn infants with birth weights between 500 g and 1500 g and gestational age ≤32 weeks who were born in a tertiary hospital between August 2006 and April 2008. We excluded infants who had died and infants who had peri-intraventricular hemorrhage grade 3 or 4, retinopathy of prematurity stage 2 or more, Doppler measurements that were not adequately obtained (failure or irregular pulsate wave in three separate measures), eyelid lesions (hemangiomas, tumors) that made examination impossible, and congenital infectious diseases.

Variables measured were systolic and diastolic velocities, pulsatility and resistance indices in the ophthalmic artery bilaterally in the first 24 hours of life and at 7 and 28 days of life, and hospital discharge in all included newborns.

We used ultrasound (LOGIQ 5; GE Healthcare, Little Chalfont, Buckinghamshire, UK) with a 7.5-MHz transducer. Examination was performed with the eyelids closed and sterile ophthalmic eye drops of 2% methylcellulose, and the transducer was positioned horizontally on the eyelids, avoiding excessive pressure on the eye so as not to cause an increase in intraocular pressure or discomfort. The ophthalmic artery was identified medially to the optic disc. Examination was performed between feedings, with the patient asleep and in the supine position and with the head fixed and centralized. Ophthalmic artery measurements were obtained with homogeneous blood flow wave patterns over 10 cardiac cycles and very good clear signals (Fig. 1). All Doppler ultrasounds were performed by the same investigator (CRSS), according to described techniques.9–15

Informed consent was obtained from the father, mother, or legal guardian of the newborn, and the study was approved by the research ethics committee of the institution. Our study adhered to the Declaration of Helsinki.

Statistical Analysis

Analysis and processing data were performed with a statistical software program (SPSS version 15.0; SPSS Inc., Chicago, IL). Calculations of sample size were made by estimating the mean values of Doppler with an accuracy of 5%, as a departure from the average of reference and with a confidence level of 95%, and from the minimum number of 44 patients.8 Continuous variables were presented as median or mean ± SD, and categorical measures were presented in absolute and relative frequencies. We used paired t-test for analysis of Doppler-derived measures of the same patient, χ² tests, and repeated-measures ANOVA for measures obtained over time.
RESULTS

From August 2006 to April 2008, 85 newborns became eligible for the study. Thirty-nine were excluded for the following reasons: 25 because of death, 8 because of retinopathy of prematurity grade 2 or 3, and 6 because of peri-intraventricular hemorrhage grade 3 or 4.

Forty-six newborns (92 eyes) were included in the study; Doppler ultrasound was performed longitudinally. Mean gestational age and birth weight were 30.4 ± 1.3 weeks and 1215 ± 202 g, respectively. Seventeen newborns (36.9%) had respiratory distress syndrome, 25 (54.3%) were small for gestational age, 6 (13%) received surfactant prophylactic treatment at birth, 15 (32.6%) received surfactant rescue treatment, and 4 (8.7%) developed bronchopulmonary dysplasia. Target hemoglobin saturation for all newborns during the whole period was 89% to 92% when they needed oxygen therapy. Data on systemic, cardiovascular, and ventilatory conditions at examination are in Table 1.

The last ophthalmic artery Doppler ultrasound (hospital discharge) was performed at 37.7 ± 0.25 weeks' postmenstrual age (gestational age at birth plus number of weeks after birth). All newborns had normal ophthalmologic examination results, with the exception of eight who had newly developed retinopathy of prematurity stage 1.

Data on Doppler ultrasounds are in Table 2. There was a change over time in systolic and diastolic velocities; measurements on the 1st and on the 7th days were significantly lower than those on the 28th day and at hospital discharge (P < 0.001 and P < 0.02 for systolic and diastolic velocities, respectively). Doppler indices were similar during the studied period.

DISCUSSION

Our study showed a statistically significant increase in systolic and diastolic velocities with no changes in pulsatility or resistance indices in very-low-birth-weight infants from birth to 38-weeks' corrected age. The results allow defining a standard for ophthalmic artery blood flow velocities and indices during neonatal intensive care unit stays.

Lindner et al.14 assessed ophthalmic artery blood flow velocity by Doppler ultrasound in the first week of life in 15 newborns at term and 10 preterm infants born at gestational ages between 26 and 35 weeks. They found no statistically significant difference in blood flow velocity in the ophthalmic artery between full-term newborns and preterm infants.14 Holland et al.15 determined the velocity of blood flow and resistance index in the central retinal artery in a small sample of 34-weeks' corrected age premature newborns undergoing evaluation for retinopathy of prematurity. Six had no retinopathy of prematurity, 9 had retinopathy of prematurity without Plus disease, and 7 had retinopathy of prematurity with Plus disease; there were no statistically significant differences in the measures among those three groups.15 Papacciet al.7 studied 45 term healthy newborn infants from the first to the fifth day of life and measured ophthalmic and central retinal blood flow velocities, resistance index, and pulsatility index. They reported an increase of blood flow velocities and indices on the fifth day of life.7 Romagnoli et al.8 measured ophthalmic and central retinal artery blood flow velocities, resistance index, and pulsatility index on days 1, 3, 5, and 7 of life in 41 healthy term newborns. Both blood flow velocities and resistance index increased significantly from the third to seventh postnatal days in both arteries.8 Our results are in very-low-birth-weight infants studied longitudinally from birth to hospital discharge. There are no published data in very-low-birth-weight infants followed longitudinally, and the published data do not allow comparison with our findings. Very preterm infants do not grow after an intrauterine growth curve, and when they reach the term they are smaller than normal term infants.10 They also develop several morbidities during their hospital stays; hence, the findings at 38 postmenstrual weeks are not comparable to those of normal term infants.

Our study set a longitudinal standard for normal systolic and diastolic velocities, pulsatility, and resistance indices during

### Table 1. Systemic, Cardiovascular, and Ventilatory Conditions of the Examined Newborns

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 28</th>
<th>Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, g</td>
<td>1215 ± 202</td>
<td>1113 ± 172</td>
<td>1543 ± 265</td>
<td>2147 ± 352</td>
</tr>
<tr>
<td>Postmenstrual age, wk</td>
<td>30.4 ± 1.3</td>
<td>31.4 ± 1.4</td>
<td>34.4 ± 1.3</td>
<td>37.7 ± 2.6</td>
</tr>
<tr>
<td>Oxygen saturation, %</td>
<td>91.7 ± 3.3</td>
<td>95.7 ± 2.3</td>
<td>94.9 ± 2.2</td>
<td>98.1 ± 1.4</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>14.8 ± 1.6</td>
<td>13.4 ± 1.2</td>
<td>11.8 ± 1.6</td>
<td>10.6 ± 1.2</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mm Hg</td>
<td>44.3 ± 7.6</td>
<td>49.1 ± 8.8</td>
<td>46.5 ± 7.1</td>
<td>45.1 ± 5.4</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>15 (32.6)</td>
<td>4 (8.7)</td>
<td>2 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Nasal CPAP, n (%)</td>
<td>27 (58.7)</td>
<td>20 (43.4)</td>
<td>10 (21.7)</td>
<td>0</td>
</tr>
<tr>
<td>Out of oxygen, n (%)</td>
<td>0</td>
<td>30 (65.2)</td>
<td>39 (85)</td>
<td>46 (100)</td>
</tr>
</tbody>
</table>

Unless otherwise noted, values are expressed as mean ± SD.
hospital stays in the neonatal intensive care unit from birth to 38 weeks' postmenstrual age.

We want to stress that eye Doppler ultrasound is an innocuous, rapid, and very easy examination to perform in very-low-birth-weight infants. Currently, the clinical detection of retinopathy of prematurity is limited to indirect ophthalmoscopy, a technique that requires a skilled and experienced examiner and carries the possibility of significant morbidity. Because retinopathy of prematurity is a vascular-circulatory disease, we suggest that further studies are needed to associate changes in ophthalmic artery blood flow as an early predictor for retinopathy of prematurity. We were unable to determine an association between ophthalmic artery blood flow and severe retinopathy of prematurity because of the small number of patients with that disorder in our unit. We have a strict guideline for oxygen therapy in preterm neonates, and threshold retinopathy of prematurity disease occurs in only 2.5% of the very-low-birth-weight infants.

In our study we used conventional ultrasound, which is limited to assessment of vascular development, especially when the oculociliary blood flow may not be detectable at very low frequencies. Doppler ultrasound with high frequencies would be more useful, but its use is still limited in humans. The mouse eye appears to be a good model to evaluate vascular development. Ultrasound biomicroscopy uses higher frequencies than conventional ultrasound, providing anatomic and functional information about in vivo mouse ocular structures. Vascular development can also be assessed with high-frequency Doppler imaging, which permits detection and characterization of ocular blood flow not detectable at lower conventional Doppler frequencies.

We suggest that Doppler ultrasound examination of the ophthalmic artery is feasible in very-low-birth-weight infants admitted to the neonatal intensive care unit. Examination should be performed with the newborn out of feeding time and asleep and under normal systemic and cardiovascular conditions. The data collected in our population describe a typical pattern of ophthalmic artery blood flow velocity, pulsatility index, and resistance index during the neonatal period in very-low-birth-weight infants. These data should be used when one suspects vascular-circulatory disorders of the eye.

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**References**


