Ophthalmic Artery Doppler Waveform in the Newborn

Satoru Iwashima, MD, PhD; Takamichi Ishikawa, MD, PhD

Background: The ophthalmic artery Doppler waveform (OADW) is thought to correlate with severity of systemic atherosclerosis. The goal of the present study was to evaluate risk of cardiovascular disease (CVD) in newborns small for gestational age (SGA) and appropriate for gestational age (AGA).

Methods and Results: A total of 15 SGA and 26 AGA newborns were enrolled in the study. OADW was compared between SGA and AGA groups. The median Doppler maximums of both eyes in the SGA group were significantly smaller than in the AGA group (maximum average velocity (max A) 6.4 cm/s vs. 8.3 cm/s, P=0.028; maximum end diastolic velocity (max D) 2.2 cm/s vs. 3.4 cm/s, P=0.003). The maximums of both eyes for the maximum resistivity index (max RI) and maximum pulsatility index (max PI) in the SGA group were significantly greater than in the AGA group (RI, 0.88 vs. 0.82, P=0.006; PI, 2.23 vs. 1.72, P=0.002). When a multiple linear regression analysis of the SGA group with a stepwise procedure was applied to positive variables from 2-sided comparisons, significant correlations were noted for max A and max PI (max A: R²=0.495, β=0.541, P=0.034; max PI: β=-3.318, P=0.012).

Conclusions: OADW in SGA newborns may be related to future risk of CVD, which is undetectable in infancy, and can provide information to estimate future cardiovascular health. (Circ J 2012; 76: 2009–2014)

Key Words: Cardiovascular disease risk; Ophthalmic artery Doppler waveform; Small for gestational age

Although cardiovascular disease (CVD), including coronary artery disease (CAD), aortic atherosclerosis and cerebrovascular disease, generally manifests in adulthood, the process of atherosclerosis can begin early in childhood. Increasing evidence shows that low birth weight (LBW) infants are at risk of hypertension in adulthood. This observation has led to the hypothesis that LBW infants who survive infancy and childhood might be at increased risk of CVD as adults. In 1989 Barker et al first postulated that LBW might be associated with undernutrition during pregnancy, and may increase the risk of abnormal lipid profile, diabetes and CVD in adulthood. In addition, small for gestational age (SGA) newborns are more likely to have metabolic abnormalities that are associated with the later development of hypertension and CAD, including insulin resistance.

The ophthalmic artery (OA) is the first major branch of the internal carotid artery and divides into many branches in the orbital area. Doppler imaging of OA provides anatomical advantages due to the vertical angle to the body surface and absence of ultrasonic obstacles. It is thought that the OA Doppler waveform (OADW) indices correlate with severity of systemic atherosclerosis in adults. Recently, Maruyoshi et al reported that waveform indices of OA were clinically useful for evaluating the severity of CAD. Novel OADW findings have been used also in clinical situations, and severity of atherosclerosis of the retinal arteries strongly correlates with plasma total cholesterol, low-density lipoprotein cholesterol, triglycerides, and apolipoprotein-B levels but not lipoprotein (a). Another study showed that the diastolic blood flow pattern in OADW was significantly flattened in diabetic patients with CAD compared with those without CAD. OADW is used predominantly for evaluating ocular vascular disease. The technical reproducibility of OA Doppler imaging has been well established in the ophthalmological field by sufficient observer experience. The goal of the present study was to evaluate the future risk of CVD in SGA infants compared with appropriate for gestational age (AGA) infants using OADW measurements in the newborn.

Methods

Subjects

Subjects were patients admitted to the neonatal intensive care units of Hamamatsu University School of Medicine Department between August 2003 and July 2010. Excluded were twins and infants with congenital disease, on ventilators, or having chromosomal abnormalities. We excluded subjects who had findings of retinopathy of prematurity (ROP) diagnosed by an ophthalmologist when initial retinal screening was performed at 4–8 weeks after birth. No patient was treated with inotropic drugs. Also, patients who had poor systolic performance with...
Ultrasound Evaluation of OA Blood Flow Velocity

Spontaneous closure of the patent arterial duct was confirmed on color Doppler echocardiography before the OADW ultrasound examination in all cases. Echocardiography measurements were performed on infants in the resting state. Figure shows the OADW at the eyeball. We attached the probe on the newborn’s eyelid as carefully as possible and checked heart rate (HR; beats/min) and respiration rate; percutaneous pulse oximetry (SpO₂) was also monitored. During the ultrasound examinations there was no apnea attack, bradycardia, acute conjunctivitis, or other complications in any of the newborns. OADW imaging was performed by the same operator in each case, using the method of Lieb et al. Data acquisition was performed with a Toshiba SSA-550A equipped with a 7.5-MHz sector transducer (Toshiba Medical Systems, Tochigi, Japan). The Doppler sample volume was set at an axial length of 2 mm with a wall filter setting of 200–400 Hz. The sample volume marker was positioned approximately 15–20 mm from the eyelid, and the blood flow velocity of the OA was assessed on pulsed Doppler. The transducer beam was set as close to the Doppler beam as possible at an angle of 20° in selected planes. No correction was made for angle correction of the Doppler signal. Pulsed Doppler spectral analysis of OA allowed the determination of peak systolic velocity (S; cm/s), end diastolic velocity (D; cm/s), and average velocity/1 cardiac beat (A; cm/s), which were defined as the mean of the peak frequency envelope that outlines all the frequency peaks in systolic, diastolic, and all phases, respectively. OADW included S, D, A, S/D ratio, pulsatility index (PI), and resistivity index (RI). PI and RI, which are classic indices of vascular resistance, were calculated as follows: PI = [(S–D)/A], and RI = [(S–D)/S].

Three or 4 images of the best quality were chosen for each subject. The stored digital scans were analyzed by a reader blinded to the patient’s condition (S.I.).

Evaluation of Biochemical and Cardiovascular Characteristics

Fasting venous blood samples from heel pricks were drawn before feeding with human or non-human milk. Blood samples for biochemical assessments were obtained after the ultrasound was done. Duplicate blood pressure (BP) measurements were obtained on the left or right arm with the newborns in a relaxed, supine position with an automatic oscillometric cuff device (UA-787, A&D Company, Tokyo, Japan). Arm length and circumference measurements were made during the examination to ensure proper cuff size. BP in newborns was measured at the time of the ultrasound.

We measured LVFS, peak E wave, peak A wave, E/A ratio, myocardial performance index (MPI), left ventricular systolic volume index (LVSVI, ml · min⁻¹ · body surface area [BSA]⁻¹) and left ventricular cardiac output index (LVCOI; L · min⁻¹ · BSA⁻¹) on echocardiography, and by HR. The Doppler-derived MPI, which is also known as the Tei index, is a measure of the combined systolic and diastolic function of the ventricles. The MPI is defined as (a–b)/b, where “a” is the interval between the end and onset of systemic ventricular inflow, and

### Table 1. Characteristics of Newborns

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Primiparity</td>
<td>SGA (n=15) 8/15</td>
<td>AGA (n=26) 13/26</td>
</tr>
<tr>
<td>CS delivery</td>
<td>11/15</td>
<td>17/26</td>
</tr>
<tr>
<td>GA (weeks)</td>
<td>36.2 (31.0–39.6)</td>
<td>35.0 (28.0–41.6)</td>
</tr>
<tr>
<td>Age (days after birth)</td>
<td>5 (1–31)</td>
<td>4 (1–31)</td>
</tr>
<tr>
<td>Apgar score (5 min)</td>
<td>9 (9–10)</td>
<td>9 (8–10)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>42.0 (37.4–46.0)</td>
<td>45.0 (35.0–50.0)</td>
</tr>
<tr>
<td>Weight (g)</td>
<td>1,680 (1,260–2,176)</td>
<td>2,392 (996–3,258)</td>
</tr>
<tr>
<td>WBC (μl)</td>
<td>9,100 (6,700–28,600)</td>
<td>11,050 (5,900–22,100)</td>
</tr>
<tr>
<td>HB (g/dl)</td>
<td>17.5 (12.1–21.7)</td>
<td>15.7 (10.0–21.8)</td>
</tr>
<tr>
<td>Ht (%)</td>
<td>50.2 (33.5–61.0)</td>
<td>47.6 (29.9–64.0)</td>
</tr>
<tr>
<td>pH</td>
<td>7.359 (7.255–7.488)</td>
<td>7.366 (7.279–7.508)</td>
</tr>
<tr>
<td>PCO₂ (mmHg)</td>
<td>43.5 (28.7–50.2)</td>
<td>37.8 (23.3–58.4)</td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>5.3 (4.4–6.0)</td>
<td>5.2 (4.3–6.5)</td>
</tr>
<tr>
<td>BE (mmol/L)</td>
<td>–1.0 (–6.0–4.0)</td>
<td>–3.0 (–8.0–4.0)</td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>136.0 (132.0–140.0)</td>
<td>137.0 (130.0–141.0)</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>4.4 (4.0–6.6)</td>
<td>4.5 (3.3–6.1)</td>
</tr>
<tr>
<td>i-Ca²⁺ (mmol/L)</td>
<td>1.15 (0.91–1.65)</td>
<td>1.06 (0.81–1.31)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.1 (0.1–0.7)</td>
<td>0.1 (0.1–0.7)</td>
</tr>
<tr>
<td>BS (mg/dl)</td>
<td>62.0 (34.0–101.0)</td>
<td>67.0 (39.0–109.0)</td>
</tr>
</tbody>
</table>

OGA, small for gestational age; AGA, appropriate for gestational age; CS, cesarean section; GA, gestational age; WBC, white blood cell; HB, hemoglobin; Ht, hematocrit; TP, total protein; BE, base excess; CRP, C-reactive protein; BS, blood sugar.

left ventricular fractional shortening (LVFS) <25% on echocardiography were excluded. There was a total of 41 infants in the study. The characteristics of the study patients are summarized in Table 1. Primary diagnosis was 15 infants with LBW <2,300 g, 12 with transient tachypnea of newborn, 5 with respiratory distress syndrome, 4 with massive aspiration syndrome, 4 with infection, and 1 with newborn pneumothorax.

Informed consent was obtained from parents or legal guardians of the infants before examination. The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine. The study was conducted according to the principles of the Declaration of Helsinki.
“b” is the ejection time of the systemic outflow according to pulsed Doppler measurements. LVSVI and LVCOI were obtained on pulsed Doppler measurements. The transmitral flow velocity was recorded from the apical 4-chamber or apical long-axis view with the pulsed wave Doppler sample volume positioned at the tips of the mitral leaflets during diastole. LVFS was obtained on M-mode echocardiography.

**Comparison of SGA and AGA Infants**

Newborns were categorized as either SGA or AGA. Birth weight was determined as being below or above the 10th percentile for gestational age from the Japanese gestational age-specific reference for birth weight based on a nationwide population.

**Statistical Analysis**

Results are expressed as median and range. We compared the biochemical and cardiovascular characteristics of the SGA group with the AGA group including echocardiography measurements. We used right and left OADW data, for which 3 or
4 images of the best quality were chosen for each eye, and the max OADW was defined as the higher OADW between the right and left eyes. OADW included S, D, A, S/D ratio, PI, and RI. Two-sided comparisons were made using the Mann-Whitney U-test and the Yates corrected chi-square test. Variables identified on univariate analysis between the SGA group and AGA group were used for multivariate analysis using stepwise logistic regression with forward selection and backward elimination. For all statistical analyses, P<0.05 was considered significant. Statistical analysis was done using SPSS version 11.0 J (SPSS, Tokyo, Japan).

Results

Table 1 lists the clinical and biochemical characteristics of the 15 SGA and 26 AGA newborns in the present study. There was no statistically significant difference in biochemical characteristics between the 2 groups. Table 2 lists the comparison of cardiovascular characteristics in the 2 groups. There was no statistically significant difference between the 2 groups in HR, BP, systolic cardiac function, diastolic cardiac function, MPI, LVSVI, or LVCOI.

We compared the eyeball size in the 2 groups, as measured using the diameter of the longitudinal axis from 12 to 6 o’clock and diameter of the horizontal axis from 9 to 3 o’clock; there were no differences in eyeball size (median, range) between the 2 groups (SGA vs. AGA, right eye longitudinal measurement: 15.5 mm, 13.4–17.2 mm vs. 16.5 mm, 14.2–17.8 mm, P=0.051; right eye horizontal measurement: 14.6 mm, 11.9–17.1 mm vs. 15.3 mm, 12.1–17.2 mm, P=0.06; left eye longitudinal measurement: 15.6 mm, 13.1–19.4 mm vs. 16.1 mm, 14.0–18.4 mm, P=0.184; left eye horizontal measurement: 14.8 mm, 12.0–17.4 mm vs. 15.0 mm, 13.0–17.4 mm, P=0.267).

Table 3 summarizes the OADW measurements in the 2 groups. Right A and D in the SGA group were significantly lower than in the AGA group. The right eye RI and PI in the SGA group were significantly higher than in the AGA group. Left D in the SGA group was significantly lower than in the AGA group. The left, that is, the S/D ratio, RI, and PI, in the SGA group were significantly higher than in the AGA group. Median (range) for the Doppler maximum of both eyes in the SGA group was significantly lower than in the AGA group (max A: 6.4 cm/s, 4.5–11.5 cm/s vs. 8.3 cm/s, 3.9–14.2 cm/s, P=0.028; max D: 2.2 cm/s, 1.7–5.2 cm/s vs. 3.4 cm/s, 1.7–6.0 cm/s, P=0.003). With regard to maximums for both eyes, the S/D ratio, RI, and PI in the SGA group were significantly higher than in the AGA group (max S/D ratio: 7.1, 5.0–10.4 vs. 5.3, 2.9–8.3, P=0.004; RI: 0.88, 0.80–1.03 vs. 0.82, 0.70–0.92, P=0.005; PI: 2.23, 1.51–2.85 vs. 1.72, 1.19–2.39, P=0.002).

Results of the multiple regression analysis are given in Table 4.

When a multiple linear regression analysis for the SGA group with a stepwise procedure was applied to positive variables from 2-sided comparisons, as independent variables, significant correlations were noted for max A and max PI (max A: R²=0.495, β=0.541, P=0.034; max PI: β=−3.318, P=0.012).

Discussion

There were no significant differences in biochemical and cardiovascular parameters between the SGA group and AGA group, including BP, but there were significant differences in some parameters of OADW. There was no significant differ-
ence in max S wave between the SGA and AGA groups but there were significant differences in max A wave, max D wave, S/D ratio, max PI, and max RI between the 2 groups. Multiple stepwise regression analysis of OADW showed a significant difference in max A and max PI between the SGA and AGA groups. The precise mechanism underlying this finding remains unknown, although several potential mechanisms can be suggested. Arteries perform both a conduit function and a pooling function for part of the ejection blood flow from the left ventricle, as well as storing part of the systolic volume during systole and draining it during diastole. Thus, this so-called “Windkessel function” transforms the pulsatile flow of the central arteries into the steady flow required in the peripheral tissues. When there is decreased arterial distensibility, a greater proportion of the stroke volume is forwarded to the peripheral circulation, and less can be cushioned in the arterial bed during systole, and the amplitude of the arterial pulse wave and, therefore, systolic BP is increased. Consequently, at a given vascular resistance, the fall in diastolic BP will also be greater if the stiffness of the large arteries is increased. In the present study, BP, LVSVI and LVCOI in the SGA group were not significantly different from the AGA group, but the OADW was significantly different between the SGA and AGA groups. The differences observed between max A and max PI of OADW reflect an atherosclerotic-like condition that indicates the possibility of CVD risk from the prenatal period. These data suggest that prenatal events could predispose an individual to cardiovascular risk in later life.

We assessed the CVD risk factors between the SGA and AGA newborns using OADW with non-invasive ultrasound techniques. LBW caused by preterm birth or SGA or both is known to be associated with increased rates of CVD and non-insulin-dependent status in adult life. In 2005, Skilton et al presented interesting information concerning a possible mechanism whereby SGA newborns may be predisposed to develop CVD later in life. In SGA infants abdominal artery intimal-medial thickness was significantly greater than in the control subjects. Better management of undernutrition during gestation and a focus on neonatal growth during the early postnatal period may be important factors to improve future health. Of note, in a large epidemiologic study, the risk of hypertension in adulthood was correlated with the degree of gestational immaturity. These findings are in agreement with the wider concept of the developmental origins of cardiovascular and metabolic disease, which relate to a particular window of vulnerability. Pathological findings suggest that arterial stiffness could be caused by a deficiency in elastin synthesis in the wall of the aorta and in the large arteries. The elastic properties of the aorta are determined by elastin, a major component of the extracellular matrix in the media of the vessel wall. Elastin normally accumulates in the late prenatal period and its synthesis falls rapidly after birth. The half-life of elastin turnover was postulated to be 40 years for the umbilical artery elastin content, a possible proxy for systemic fetal elastin content. This is because umbilical arteries are direct branches of the fetal iliac arteries. A study found that a strong correlation exists between gestational age and elastin content; a reduction in elastin content of the umbilical cord arteries was observed both in preterm and SGA newborns. Interestingly, Burkhart et al recently reported increased arterial stiffness with decreased elastin content in the umbilical arteries from SGA infants. In a rat study in which the offspring were nutrient restricted utero, Khorram et al observed a significant remodeling of the extracellular matrix of the aorta, resulting in increased stiffness.

The present data suggest that OADW of newborns can provide new information to predict future cardiovascular health. Several limitations in the present study should be addressed. This study was conducted with a relatively small number of patients, and used a cross-sectional study design. Although there were a few preterm newborns in the present study, we included as many normal near preterm newborns as possible. We could not follow up all newborns with CVD risk factors in the long term. The relationship between the vascular changes on the ocular fundus and OA Doppler imaging could not be investigated because of the lack of fundoscopy data. Further comparative studies are needed to determine whether there is a relationship between ocular fundus findings and OA Doppler flow, given that OA Doppler flow is highly suggestive of systemic atherosclerosis. In the present study clinical conditions may have influenced the OADW, especially during the transition from the fetal to the newborn state. In the present data some infants with transient tachypnea and respiratory distress syndrome were LBW. Therefore, we could not compare OADW differences according to the clinical conditions. The OADW between SGA and AGA groups having similar clinical conditions, however, including baseline blood results and cardiac function on ultrasound, was compared. We compared the biochemical and cardiovascular characteristics of the SGA group with the AGA group, including echocardiography measurements.

We could not show that the pulse pressure of SGA newborns was higher than in AGA newborns; therefore, the present results indicate that there was no significant difference in stiffness of the aorta between SGA and AGA newborns. We did, however, show that BP did not differ significantly between SGA and AGA, even though there were clear differences in body size between the 2 groups. In neonates, body size can reflect BP. This might indicate that arterial stiffness in SGA infants was increased more than in AGA infants, but because this study was conducted with a relatively small number of patients. Further studies are needed on CVD risk in SGA neonates over the long-term and further comparative studies are needed to elucidate the relationship between ocular fundus findings and OADW, which may be highly suggestive of systemic atherosclerosis.

In the present report, several references were made to Barker’s hypothesis with regard to LBW infants, but it was beyond the scope of this study to follow up all newborns with CVD risk factors over the long term and therefore provide data to support or refute Barker’s hypothesis. Recently, however, the mechanism of developmental origins of health and disease (DOHaD), including mediating metabolic and hormonal factors, has been investigated. The concept of DOHaD has provided us with a new approach to the prevention of CVD. Further studies are necessary over a longer period of time to define the risk factors for CVD and metabolic syndrome in children. In addition, prospectively designed studies might demonstrate further the clinical value of OA Doppler imaging to estimate cardiovascular function.

In conclusion, the present novel findings suggest that OADW of newborns can provide new information to estimate cardiovascular function. It appears that OADW in preterm newborns with SGA may have some latent link to future risk of CVD, which is otherwise undetectable in infancy.

References


