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ORIGINAL ARTICLE

Relationship between birth weight and retinal microvasculature in newborn infants

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Objective: The purposes of this study were to determine the normal retinal microvasculature measurements in human infants who are born at term and to determine whether birth weight influences measurements of retinal microvasculature.

Study Design: Retinal arteriole and venule measurements were obtained in a cohort of 24 infants who were born at term. Digital images of both the retinas were obtained using a digital retinal camera after pupillary dilation.

Result: In all, 24 newborn infants born at term (12 females and 12 males) were analyzed in this study. The measured retinal arteriole diameters were from 66.8 to 147.8 μm (mean, 94.2 ± 19.6 μm), and the venule diameters were from 102.0 to 167.8 μm (mean, 135.2 ± 19.1 μm). Seven babies in the sample had low birth weight (LBW), while 17 babies were born with normal weight. Babies with lower birth weights had larger arteriole (113.1 ± 17.9 μm vs 86.4 ± 14.4 μm; $P = 0.0009$) and venule diameters (151.7 ± 14.9 μm vs 128.4 ± 16.9 μm; $P = 0.0040$).

Conclusion: Retinal venules and arterioles in LBW babies are larger compared with those of normal-birth-weight babies. We postulate that the difference observed in our study was due to *in utero* pathophysiological changes that occurred in the cerebral circulation of growth-restricted fetuses.

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Introduction

In utero insults that result in low-birth-weight (LBW) infants (birth weight < 2500 g)[1] are now well recognized as risk factors contributing to the development of vascular-related diseases in adulthood.[2–6] LBW infants are a heterogeneous group of infants, comprising infants who are premature (< 37 completed weeks of gestation),[1] growth-restricted (weight below the 10th percentile for their gestational age)[1] or a combination of both. The exact mechanism of this phenomenon has yet to be fully understood, but there is increasing evidence to suggest that microcirculatory pathology forms the mechanistic link between fetal insult and the adult manifestation of illness.[7–11] The challenge has been to investigate microcirculatory changes *in vivo*. The retina provides an opportunity for *in vivo* investigation of human microcirculation, and changes in the retinal vessels have been identified in some individuals who had LBW as infants and later developed hypertension, ischemic heart disease, stroke and renal disease.[9,12–15] The ability of retinal-imaging technology to assess and measure the retinal microvasculature makes this a very valuable assessment tool.[16–18] Studies involving young children, adolescents and adults who were born small have shown abnormalities in the retinal vasculature.[9,12,15,19–23]

Although the retinal microvascular of premature infants is routinely assessed to detect and treat retinopathy of prematurity,[24] there are no published studies regarding the use of retinal-imaging technology to assess the retinal microvasculature of at-term, growth-restricted infants. There are also no published data concerning normal measurements of retinal microvasculature in infants. The purpose of the present study was to determine normal measurements of the retinal microvasculature in human infants who are born at term. This study also investigated whether birth weight influences measurements of retinal microvasculature.

Methods

This study was performed in the Department of Neonatology, The Townsville Hospital, Douglas, QLD, Australia. The Department of Neonatology is a tertiary perinatal center catering to more than 10 000 births each year. The study commenced in August 2010, and the data presented in this study are based on patients recruited until May 2011. This study was approved by the Townsville Health District Human Research Ethics Committee. Written parental consent was obtained, and babies with syndromes, prematurity and chromosomal abnormalities were excluded. All assessments were

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performed within the first 7 days of life. Babies with birth weights of $\leqslant 2500$ g were classified as LBW babies, and babies weighing from 2501 to 4500 g were classified as appropriate for gestational age babies. Only babies who were born at term (37 weeks of gestation completed) were included in this study.

After pupillary dilation, digital images of both the retinas were obtained using a digital retinal camera (RetCam, Massie Laboratories, Dublin, CA, USA). Measurements of the diameters of retinal vessels were then obtained using a predetermined protocol that first involved the identification of retinal vessels located from 0.5 to 1 disc diameter from the margin of the optic disc (Figure 1). Measurements of vessel diameter were then obtained using semi-automated software (Vesselmap, IMEDOS GmbH, Jena, Germany).[25,26] Vascular diameter was computed as wall-to-wall distance within the vessel. The caliber of directly viewed vessels was determined by the size of the red-cell column, because the vessel walls and peripheral plasma layer are nearly transparent.[27] Measurements of vessels from each eye were obtained, and the largest venule and arteriole for each patient was determined. These measurements were then used for analysis. An intra-class correlation coefficient was used to determine the reliability of this technique;[28] this correlation coefficient was 0.90 (95% confidence interval of 0.75 to 0.96). A previously published study in infants has shown that the blood flow in the central retinal arteries is similar in both the eyes.[29]

In adult eyes, correction can be applied to compensate for inaccuracies in the measurements of retinal structure that occur because of refractive error; this correction requires parameters such as axial length and keratometry (curvature of the anterior surface of the cornea) to be known.[30] In infants, these calculations are more challenging because obtaining these measurements is difficult and the eye is continuing to grow.[30] Statistical analysis was carried out using Stata ver. 11.0 (Stata, College Station, TX, USA). Using Student's *t*-test, *P* values <0.05 were considered significant.

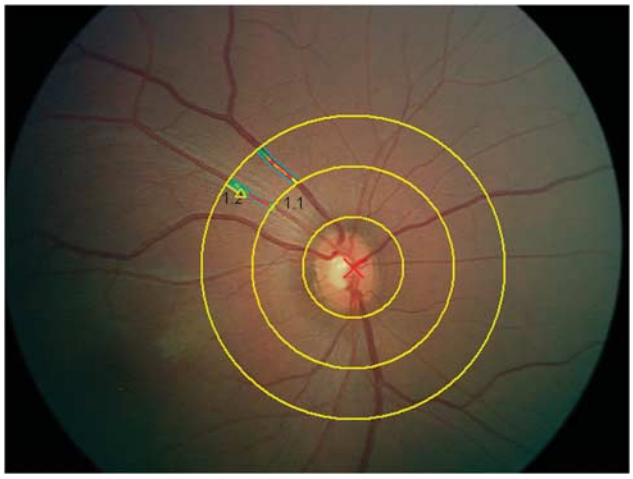

Figure 1 Retinal image from a newborn infant showing identification and measurement of retinal vessels from 0.5 to 1.0 disc diameters from the margin of the optic disc.

Results

A total of 247 babies were admitted to the department during the study period. Of these, 99 were suitable for recruitment, and their parents were approached for participation. Written consent was obtained for 24. All 24 newborn infants born at term (12 females and 12 males) were analyzed in this study. Birth weights ranged from 1845 to 4310 g (mean, 3029 ± 649 g) with gestational ages of 37 to 41.6 weeks (mean, 38.7 ± 1.4 weeks). Retinal arteriole diameters were from 66.8 to 147.8 μm (mean, 94.2 ± 19.6 μm), and venule diameters were from 102.0 to 167.8 μm (mean, 135.2 ± 19.1 μm). Table 1 compares the differences in these measurements between male and female infants.

The infants were divided into two cohorts based on birth weight (LBW and appropriate for gestational age). There were 7 LBW babies and 17 appropriate for gestational age babies. Babies with LBW had larger arteriole (113.1 ± 17.9 μm vs 86.4 ± 14.4 μm; $P = 0.0009$) and venule diameters (151.7 ± 14.9 μm vs 128.4 ± 16.9 μm; $P = 0.0040$). Figures 2 and 3 show the relationship between birth weight and vessel diameters. Pearson's coefficient of correlation between retinal arteriole and venule

Table 1 Comparison of measurements between male and female infants

	Male	*Female*	P-*value*
Number	12	12	
Birth weight (g)	3017 ± 537	3041 ± 770	0.9282
Gestation (weeks)	38.3 ± 1.1	39.2 ± 1.4	0.0994
Venule diameter (μm)	130.2 ± 18.8	140.3 ± 18.9	0.2029
Arteriole diameter (μm)	90.1 ± 17.2	98.2 ± 21.6	0.3206

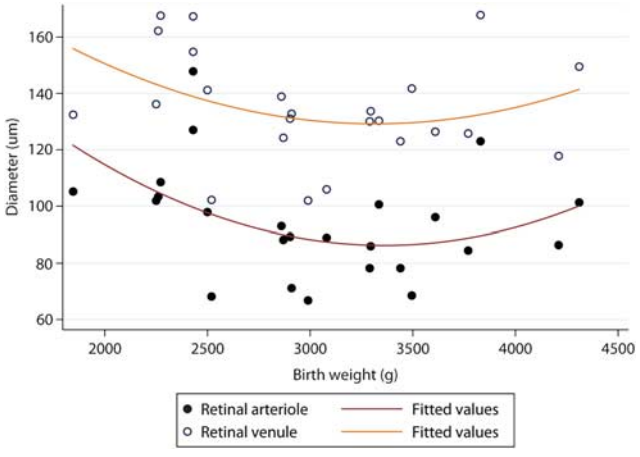

Figure 2 Relationships between birth weight and the diameters of retinal arterioles, and venules in infants born at term.

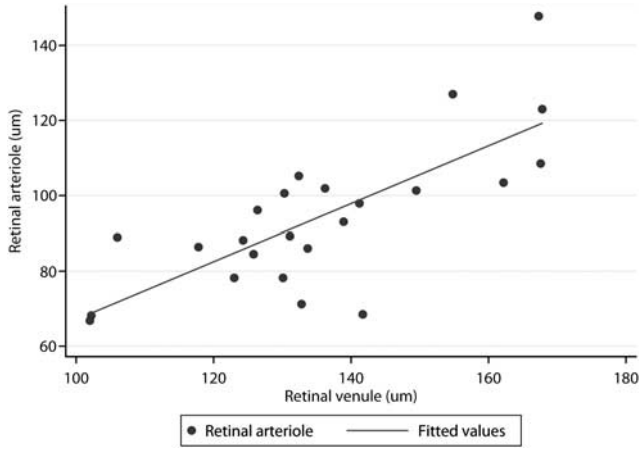

Figure 3 Increasing retinal arteriole diameter is closely correlated with increasing retinal venule diameter.

diameter was 0.7522 (95% confidence interval 0.50 to 0.89; $P<0.0001$).

Discussion

To date, studies of retinal vasculature in infants have mainly focused on premature infants and retinopathy of prematurity.[25,26] To our knowledge, this is the first study to investigate measurements of retinal microvasculature using digital retinal imaging in infants born at term. These measurements could be used as a baseline for future studies that investigate the effects of birth weight on retinal microvasculature. Previous studies have shown a strong relationship between LBW and retinal vasculature size in older children,[15,19,22,23,31] adolescents[32] and adults.[9,12,13] However, no published studies utilized baseline measurements of infant retinal vasculature for comparison. For the first time, we were able to measure retinal arteriole and venule sizes in LBW infants during infancy. The data from this study show significantly higher retinal vessel diameters in LBW babies. By contrast, previously published studies of young children[15,22] have shown that children who were born as LBW infants had narrower retinal arteriolar calibers. Narrowing of these vessels has been linked to the development of cardiovascular diseases in adults.[7,14,33]

Why are the diameters of retinal vessels significantly larger in LBW babies? Only infants born at term were reviewed in this study; thus, the cause of LBW in this cohort was intrauterine growth restriction. The retinal images in this study were all taken during the first week of life, so we propose that the differences observed in our study were due to pathophysiological changes that occurred *in utero*. There are many causes of intrauterine growth restriction, but the most common is uteroplacental insufficiency, which results in fetal hypoxia.[34,35]

Fetal cerebrovascular responses to hypoxia are fundamentally different from those observed in the cerebral circulation of adults.[36] The vasculature of the immature brain is highly plastic and can respond to hypoxia with robust increases in capillary density.[36] Endothelial vasodilator capacity is typically depressed in fetal cerebral arteries, and the endothelium contributes relatively little to hypoxic vasodilatation in the fetus.[36,37] By contrast, the endothelial contribution to hypoxic vasodilatation increases throughout early postnatal life, becoming quite prominent in the cerebral arteries of adults.[37,38] Hypoxia exerts effects on vascular smooth muscle through various mechanisms.[36] The smaller and more peripheral cerebral arteries relax quickly and completely in response to hypoxia, whereas the larger and more proximal arteries, including the common carotid, maintain muscle tone much better and have a more important role in the gradual adjustments of cerebrovascular tissue to resist hypoxia.[39]

Animal studies have provided insight into some aspects of the basic pathophysiology of intrauterine growth restriction, and studies using technologies such as Doppler ultrasound to investigate maternal and fetal vessels have added further information. Doppler ultrasound allows for the assessment of the vascular effects of placental dysfunction on the placental and fetal vasculature.[40] In response to hypoxia, the fetus uses a compensatory mechanism to redistribute cardiac output and blood supply to the brain to maintain constant blood delivery to this organ (the head-sparing effect).[41] The result is a decrease in cerebral blood-flow resistance and vasodilatation of the arteries. This effect, which can be measured using Doppler ultrasound, shows a decrease in resistance and an increase in blood flow in the middle cerebral artery.[40] Studies of growth-restricted fetuses have confirmed dilatation of the middle cerebral artery and the resulting increase in blood flow to the brain compared with fetuses with normal growth.[42–44]

Figure 4 shows the close relationship between the retinal artery and the middle cerebral artery. The endothelia of the vessels in the brain and retina are lined with continuous endothelial cells, connected by tight junctions that help to maintain the blood–brain barrier.[45] Doppler flowmetry data from newborn babies have shown that an increase in blood flow in the middle cerebral and ophthalmic artery is closely followed by an increase in blood flow in the central retinal artery.[29] Blood flow in the middle cerebral artery and cerebral blood flow are spatially and temporally coupled to fetal brain function and metabolism, and we postulate that, in a growth-restricted fetus, the same neurovascular coupling extends to the retinal artery. Dilation of the middle cerebral artery possibly results in dilatation of retinal vessels in growth-restricted, LBW infants.

The main limitation of our study was its relatively small sample size. It was also difficult to account for any refractive error that could have contributed to the results. We plan to follow this cohort over time to identify the changes in retinal vasculature as these infants grow.

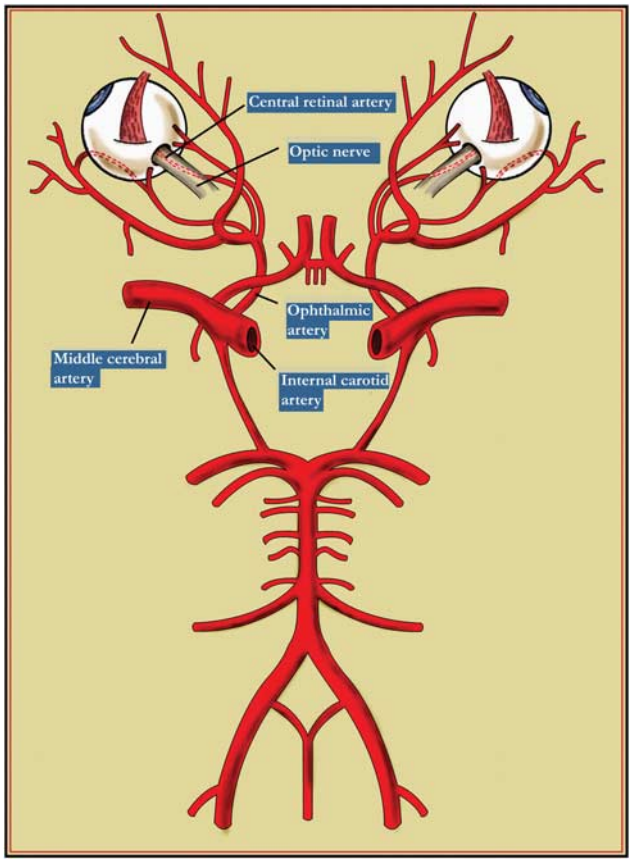

Figure 4 Diagram showing the Circle of Willis, middle cerebral artery and origin of the ophthalmic and central retinal arteries.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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