Early Life Microcirculation and the Development of Hypertension

Harry A.J. Struijker-Boudier, Bart F.J. Heijnen

See related article, pp 847–851

Research in the past decades has established a key role for the intrauterine environment, especially the maternal nutritional status, in influencing fetal growth and cardiovascular health in the offspring in later life. Experimental evidence suggests that the vasculature of the developing fetus may already be compromised by a suboptimal uterine environment. Recent data found associations between low birth weight and early vascular dysfunction, in particular in the fields of arterial wall compliance, endothelium-dependent vasodilatation, and microvascular structure. Arterial stiffness has been observed as early as on the fifth day of life in low gestational age infants. The alteration of the viscoelastic properties of conductance arteries has been attributed to an impaired vascular elastogenesis. A second mechanism considered to initiate hypertension in later life is early endothelial dysfunction. In several human studies, intrauterine growth restriction has been associated with altered endothelium-dependent vasodilatation at different ages, starting as early as in 3-month–old infants. Ligi et al have recently proposed that functional impairment of endothelial progenitor cells underlies the early endothelial dysfunction of low birth weight infants.

The third vascular abnormality implicated has been microvascular remodeling, including reduced density of arterioles and capillaries. Microvascular remodeling has been studied most extensively using the retina as a target organ. In a series of studies, Sasongko et al have shown that smaller birth size is associated with narrower retinal arterioles in 6-year–old children, in early adolescence, and in adults. Sasongko et al hypothesized that arteriolar narrowing is an adaptive response to the acute hyperoxgenation that preterm infants experience immediately after birth. Furthermore, hyperoxia would downregulate the expression of vascular endothelial growth factor and initiate obliteration of retinal capillaries, causing an increased capillary-free zone of the retina. They speculate that, although this theory refers to preterm infants, it may also be applicable to infants born mature but with low birth weight. Studies on the retinal microcirculation in newborns, which could substantiate this speculation, have not yet been reported, probably because of technical limitations.

Reduced density of arterioles and capillaries is widely considered to play a key role in the development of hypertension. Low birth weight, after either preterm birth or intrauterine growth restriction, has been associated with a decreased arteriolar and capillary density in the retina, as well as the skin microvasculature, both in children and adults. Impaired growth of the microvasculature distorts the development of several organs, including the kidney. The impaired renal development (reduced nephron number) is regarded as an important link with later hypertension development.

In this issue of Hypertension, D’Souza et al report an unexpected result. Although one would expect, on the basis of the evidence discussed above, that low birth weight infants would have significant skin capillary rarefaction at birth, they find the opposite: a significantly higher capillary density. D’Souza et al made this observation in 44 low birth weight children born to normotensive mothers either preterm or at term compared with 71 infants born at term with normal weight. The observations were made using orthogonal polarized spectroscopy to measure basal (ie, functional) and maximal (ie, structural) skin capillary density. Orthogonal polarized spectroscopy is a relatively new method that allows the noninvasive measurement of the microcirculation in the skin of infants as young as 1 to 4 days postnatally. The unique feature of this study is the very early noninvasive microvascular observations. This feature distinguishes the study from the previous retinal observations that were made in young children (6–8 years), adolescents, or, mostly, adults. The different age may be one explanation for the discrepancy between the observations by D’Souza et al and previous results (summarized by Sasongko et al and Clough and Norman). D’Souza et al measured capillary density immediately after birth when capillary density is relatively high compared with later stages in life. In low birth weight infants, the density may even be higher because of the relative systemic hypoxia that these infants experience in utero. Basal capillary density decreases progressively after the first week of life because of a process of pruning. It may be speculated that low birth weight infants undergo a process of capillary hyperpruning because of a relative hyperoxia of the extraterine environment, together with supplemental oxygen in the postnatal period of preterm infants. Alternatively, a “catch-up” process with abundant availability of nutrients may cause capillary hyperpruning. Third, low serum levels of insulin-like growth factor 1, an important vascular growth factor during the first weeks or months of life, were recently shown in low birth weight infants. D’Souza et al could...
obtain further evidence for the capillary hyperpruning hypothesis if they follow up their cohort of low and normal birth weight infants for 3-, 6-, and 12-month periods postnatally.

An important consequence of the observations made by D’Souza et al.\(^\text{12}\) is that the capillary rarefaction seen in adults, although it might be programmed in utero, occurs remotely from birth. Therefore, genetic or epigenetic factors, rather than low birth weight, per se, may be involved. Evidence for a genetic factor, rather than low birth weight, was obtained recently in a study on twins.\(^\text{15}\) Studies in genetic rat models of hypertension have stressed the importance of a critical time window in the postnatal period in which genetic factors determine structurally based changes in vascular resistance in the kidney.\(^\text{16,17}\) The intrarenal renin-angiotensin-aldosterone system plays a particularly important role in this postnatal microvascular development, because a brief period of treatment with renin-angiotensin-aldosterone system blockers can prevent the development of hypertension for a prolonged period of time.\(^\text{16}\)

In summary, the technically elegant observations by D’Souza et al.\(^\text{12}\) suggest that events remotely from birth rather than during intrauterine life may determine the microvascular risk in low birth weight infants. This hypothesis can be further substantiated by follow-up studies in their interesting cohort of infants.

**Sources of Funding**
The research of the authors is funded by grant T2-301 of the Top Institute Pharma in The Netherlands.

**Disclosures**
None.

**References**