Retinal Microcirculation and Early Mechanisms of Hypertension

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The microcirculation plays a critical role in the pathophysiology of hypertension.1,2 The increase in peripheral resistance underlying the raised blood pressure is localized primarily in small arteries (diameter 150 to 300 μm) and arterioles (diameter 10 to 150 μm). The rise in blood pressure causes a further narrowing of small arteries and rarefaction of capillaries and precapillary arterioles, thus creating a vicious cycle. This cycle has been well documented in several animal models of hypertension. However, it has been more difficult to grasp the complete picture in humans, because of technical difficulties to evaluate the microcirculation in vivo. The study of small arteries in humans is based on biopsies usually taken from subcutaneous fat tissue. Using this approach Rizzoni et al3,4 were able to show that small artery narrowing predicts the prevalence of cardiovascular complications in both normotensive and hypertensive individuals. Capillary rarefaction has been assessed in humans using in vivo capillaroscopy of the nailfold microvasculature. The majority of these studies support the hypothesis of capillary rarefaction as an early hallmark of hypertension.1,5,6 In the last few years, advances in retinal photography and computing technologies have enabled objective measurement of small artery and arteriolar vessel size from digital retinal images. Several large population-based studies have applied this approach to quantitatively determine retinal vessel diameters and have documented a consistent association between elevated blood pressure and narrowed retinal arterioles.7–9 Similar studies also indicated that retinal arteriolar narrowing predicts the future blood pressure elevation in previously normotensive persons.10–12

The paper by Liew et al in this issue of *Hypertension*13 extends this hypothesis by reporting that low birth weight is associated with narrower retinal arterioles in adults. The study was based on 3800 persons from the Atherosclerotic Risk in Communities study (ARIC). The association between lower birth weight and narrower retinal arteriolar caliber was also present in persons without hypertension or diabetes. This study gives further support to the hypothesis originally formulated by Barker et al14 that low birth weight is associated with a number of risk factors for cardiovascular disease, including hypertension, at adult age. Although several studies in the past years have shown that persons with lower birth weight have high blood pressure in both childhood and adulthood, the vascular mechanisms underlying this relationship are not known.15,16 The study by Liew et al suggests that intrauterine influences such as nutritional restriction, of which low birth weight is a consequence, result in structural cardiovascular changes which are adaptive in fetal life but maladaptive in adulthood.17 However, the observation that there is an association between low birth weight and narrower arterioles in persons without hypertension suggests that narrower arterioles secondary to low birth weight may not be sufficient to explain the onset of clinical cardiovascular disease. Liew et al suggest that reduced nephron number, which has been associated with low birth weight, might be such an additional trigger.

The study by Liew et al13 raises several intriguing questions. The first is how intrauterine events can trigger a condition—hypertension—which is usually only expressed in adult life. One possible explanation is that even during childhood blood pressure is already elevated in low birth weight individuals. Alternatively, the microvascular structural change causing elevated resistance and pressure is compensated for by another blood pressure–lowering mechanism, such as renal fluid and salt excretion, until adult life. In that case hypertension would only occur if the compensating mechanism loses its effect at that age. Further, longitudinal studies are required to answer this question.

A second potential question is the implication of these observations for the treatment of hypertension. The low birth weight hypothesis suggests a much earlier treatment of individuals prone to develop hypertension than the present strategy following which hypertension is only treated after it has evolved. The recent TROPHY trial gives support to this idea.18 In this trial prehypertensive treatment with an angiotensin receptor blocker caused a delay in the development of hypertension. Animal studies in spontaneously hypertensive rats spontaneously hypertensive rats have provided further evidence for the effectiveness of this approach.19,20 A relatively short treatment of spontaneously hypertensive rats with drugs blocking the renin-angiotensin-aldosterone system during the postnatal weeks 4 to 8 caused a significant lowering of blood pressure and target organ damage for a period up to 1 year. The time window for such a treatment is critical, because perinatal administration of blockers of the renin-angiotensin-aldosterone system caused severely adverse effects, including malignant hypertension, probably because of an interference with perinatal development of the kidney.21

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Wong, Klein, and their coworkers have opened up a potentially important area of hypertension research. Their retinal analysis allows the study of the microcirculation in human hypertension not only with respect to pathophysiological questions but also in relation to therapeutic interventions. The retinal images can be obtained repeatedly and therefore allow longitudinal studies on pathogenic mechanisms as well as therapeutic interventions in hypertension.

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References
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