



Insights into the microvascular rarefaction of hypertension

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Comment on: Yu GZ, Aye CY, Lewandowski AJ, *et al.* Association of Maternal Antiangiogenic Profile at Birth With Early Postnatal Loss of Microvascular Density in Offspring of Hypertensive Pregnancies. *Hypertension* 2016;68:749-59.

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Hypertension is the leading contributory cause of death worldwide and is projected to affect 1.5 billion adults by 2025. Public health efforts to help prevent and effectively treat this disease have therefore become increasingly important (1).

Despite this, the pathophysiological basis of hypertension remains incompletely understood. A role for reduced capillary density (rarefaction) antedating the onset of clinical hypertension has been proposed and is supported by its finding in subjects with “high normal” blood pressure, normotensive offspring of hypertensive parents and newborn infants of hypertensive pregnancies (2). A physiological role for capillary rarefaction in generating the hypertensive state can be proposed given that capillary pressure is raised in hypertension (3), demonstrating that the resistance of hypertension is not restricted to the pre-capillary segment of the vasculature.

In this context, Yu *et al.* seek to delineate the process of perinatal microvascular rarefaction in their recent article, published in *Hypertension* (4). Supported by evidence showing that offspring of mothers with hypertension of pregnancy are more likely to develop hypertension and its sequelae in adult life (and that this risk is proportional to the severity of the mother’s hypertensive disorder), the authors aimed to investigate the timing of capillary rarefaction in offspring of hypertensive pregnancies and explore putative humoral mechanisms involved.

Capillary density was assessed using *in vivo* imaging in infants at 5 days and 3 months post-partum. In contrast to a previous study by Antonios and colleagues (2) demonstrating rarefaction in infants born to hypertensive mothers compared to normotensive controls, Yu *et al.* did

not show any significant difference between these two groups in terms of microvascular density early post-partum.

Yu’s report studied hypertensive mothers with a significantly higher BMI than those in the normotensive group and whose infants had a significantly lower birthweight Z score than normotensive controls. Nonetheless, this latter discrepancy would only have acted to reduce capillary density in these participants and both baseline differences were also present between the two groups in the Antonios study. Therefore these group heterogeneities do not explain the inconsistent findings between the studies. It is possible to explain the disparity of findings however by considering that Antonios *et al.* only found a significant difference in capillary density when venous occlusion was used to determine maximal (structural) density. They found no significant difference in capillary number when using basal (physiological) capillary density, which much more closely resembles the data acquired by Yu *et al.* in their use of axillary side field dark stream imaging (Microscan). Other differences between the two studies which may have had an impact on their findings are the use of different imaging sites (hallux versus axilla), median age at the time of measurement (1–2 versus 5 days) and the exclusion of mothers with a pre-gestational history of hypertension by Yu and colleagues.

Therefore, the two studies’ findings are not incongruous but simply reflect variation in methodology; both support no difference in physiological capillary density at birth in infants born of hypertensive pregnancies versus normotensive controls. Importantly, Yu *et al.* explores this further. They cite that the extensive remodelling of the microcirculation occurs in the first 3 months of life as a

consequence of orderly capillary loop and subpapillary network formation from an initially disordered network in the newborn as contributing to their finding of microvascular rarefaction at 3 months.

Thus the truly novel finding of this study is that, in contrast to the observation at 5 days of life, resting physiological microvascular density was reduced in 3-month-old infants born of hypertensive mothers compared to those born of normotensive parents. The greater degree of microvascular loss from 5 days to 3 months of age in the hypertensive group was present even in multivariate modelling accounting for variations in birthweight Z score, gestational age and blood pressure at birth. This represents a significant step forward in the understanding of microvascular rarefaction of hypertension that it occurs early post-partum rather than in utero.

Intriguingly, Yu *et al.* also present possible mechanistic explanations for these novel findings. Through examination of umbilical vein-derived endothelial progenitor cells, the greater microvascular loss in the hypertensive group was found to also be associated with reduced tube formation and tube branching by cultures of these cells *in vitro*. Tube formation was found to have a graded positive association with *in vivo* measures of microvascular rarefaction at 3 months, suggesting that conditions at or shortly after birth are responsible for the greater microvascular rarefaction seen in infants born of hypertensive mothers.

The reasons for this reduced angiogenic capacity of progenitor cells at birth is unclear, though Yu *et al.* investigate a possible association with circulating maternal factors in the knowledge that a four corner epidemiological design study has previously determined a familial component to the microvascular rarefaction of hypertension (5). Accordingly, Yu *et al.* found maternal soluble endoglin levels to be higher in hypertensive mothers, with soluble fms-like tyrosine kinase-1 (sFlt-1) trending higher in this population and vascular endothelial growth factor (VEGF) trending lower. There was also a positive graded association between maternal sFlt-1 at 5 days post-partum and microvessel loss in infants between 5 days and 3 months, even in normotensive pregnancies. However, as the authors diligently acknowledge, this association does not imply causation and a scenario in which circulating maternal angiogenic modulators and offspring microvascular density are mutually correlated with another key factor can be easily envisaged.

Thus, Yu *et al.* present ground-breaking data by demonstrating twice the degree of capillary loss between

5 days and 3 months post-partum in infants born of hypertensive pregnancies compared to normotensive pregnancies. Extrapolation of this conclusion to include all those with essential hypertension may be inappropriate as those born of hypertensive pregnancies may represent a distinct phenotype of this heterogeneous disease. In addition, although there was co-association with *in vitro* endothelial cell progenitor activity and circulating maternal factors, this does not infer causation, though is a thought-provoking concept. Neither microvascular flow index nor perfused vessel density data are presented as part of the *in vivo* assessment, presumably due to time constraints, though these indicators of tissue perfusion may have been of interest to further explain the physiological changes occurring between birth and 3 months.

Despite these limitations, the article represents an important step forward in our understanding of the vascular determinants of hypertension in at-risk individuals. It is anticipated that the findings will serve as a springboard for further research into the vascular pathophysiology underpinning this critically important disease.

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