Editorial Commentary

Vascular Remodeling, Retinal Arteries, and Hypertension

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Remodeling of the vasculature is an active process of structural changes that involves alterations in cellular processes, including growth, apoptosis, migration, inflammation, and production of extracellular matrix proteins, resulting in an increase in the media:lumen ratio.\(^1,^2\) Physiological remodeling is an adaptive response occurring in response to hemodynamic changes and ageing. However, when this process becomes maladaptive, it plays a role in the pathophysiology of hypertension and its complications. Increased media:lumen ratio in small resistance arteries, because of an increase in muscle mass or rearrangements of cellular and noncellular elements, increases vascular resistance to blood flow contributing to elevated blood pressure.\(^3\) These structural changes may augment vascular reactivity, which potentiates the increase in the peripheral resistance characteristic of hypertension. Convincing evidence from studies examining small arteries obtained from gluteal biopsies of patients with hypertension indicates that vascular remodeling is a characteristic feature in hypertension, that it is one of the first manifestations of target organ damage occurring before proteinuria or cardiac hypertrophy, and that it is a dynamic process that is reversible.\(^4\) Of clinical importance, the magnitude of remodeling of small arteries has prognostic significance over a 10-year period, with worse prognosis for subjects with hypertension with greater remodeling.\(^5\)

In most studies, small arteries from humans have been studied using isolated microvessels from gluteal subcutaneous tissues. Although this approach has advantages in that it allows for direct assessment of structural and functional characteristics of resistance arteries from well-characterized patients and healthy individuals, the procedure is invasive, requiring surgical incision and sutures. Using this method to perform longitudinal studies to track vascular changes over time is impractical in clinical practice. Moreover, vessel isolation from such biopsies is not always guaranteed. Accordingly, there has been enormous effort in the development of noninvasive methods for accurate assessment of vascular status in patients with hypertension and other cardiovascular, cerebrovascular, and renovascular diseases. Current techniques include applanation tonometry, acoustic transducers, Doppler ultrasound, MRI, and transthoracic echocardiography, among others.\(^6\) However, these approaches are designed to primarily examine large arteries, without providing insights into the structure and function of small vessels that are important in hypertension and associated target-organ damage.

In the present issue of *Hypertension*, studies by Harazny et al\(^7\) and Cheung et al\(^8\) provide novel contributions in the field. Using different strategies, both studies explored the vascular structure of retinal arteries in patients with cardiovascular risk factors. The beauty of these studies is that noninvasive techniques were used. Using scanning laser Doppler flowmetry and automatic full-field perfusion imaging analysis,\(^9,^10\) Harazny et al\(^7\) showed that ageing is associated with retinal vessel remodeling in normotensive but not in hypertensive subjects and that media:lumen ratio is greatest in patients with a history of cerebrovascular events. These findings extend those reported previously by Delles et al\(^{11}\) and Baker et al,\(^12\) where it was reported that endothelium-dependent vasodilation of the retinal vasculature is impaired early in essential hypertension and that it can be restored by angiotensin II receptor subtype 1 receptor blockade. The retinal vasculature is morphologically and functionally related to the cerebral vessels because of the common origin from the internal carotid artery. Accordingly, retinal vessels are useful models to obtain insight into endothelial function and vascular structure of the cerebral circulation, and noninvasive assessment of retinal artery structure provides a novel approach for cerebrovascular risk stratification.

Findings from the study of Harazny et al\(^7\) extend beyond the descriptive and predictive nature, because they provide some evidence, albeit indirect, that structural changes in retinal arteries may resemble those in small resistance arteries and that systemic blood pressure influences vascular structure in retinal arterioles similar to that in peripheral arteries. This is supported by the observations that, in the treated patients with well-controlled hypertension, media:lumen ratio was less than that in patients with uncontrolled hypertension, similar to data reported by others in small arteries from subcutaneous tissue.\(^3,^5\) If indeed it can be proven that retinal artery function and structure mirrors that of resistance arteries, as well as cerebral vessels, the potential to study the vascular (patho)biology of human hypertension using the retinal vasculature as a surrogate becomes enormous.

The usefulness of noninvasive examination of retinal arteries as a predictor of clinical cardiovascular outcomes is further explored in this issue by Cheung et al.\(^8\) Using nonmydriatic retinography and digital retinal photographs to measure retinal vessel diameter and chest MRI to study aortic distensibility, the relationship between retinal arterial narrowing and aortic stiffness in patients free of cardiovascular diseases was investigated. Findings demonstrate that increased aortic stiffness is associated with retinal arteriolar narrowing, independent of age, blood pressure levels, and...
other cardiovascular risk factors. If the alterations revealed in retinal arteries are representative of other small arteries, such changes may play a role linking aortic stiffness with clinical cardiovascular events, such as stroke, myocardial infarction, and renal failure. However not all reports support the concept that retinal arterial vascular alterations are predictive of cardiovascular disease. Recent studies failed to demonstrate a significant association between left ventricular concentric remodeling and other signs of extracardiac target organ damage, including retinal changes in patients with essential hypertension.13

Findings from the studies under consideration in this issue should be interpreted within the context of the experimental design. Although there are strengths to each study, there are some limitations that warrant further consideration. First, noninvasive assessment of retinal vessels is not a simple procedure. It requires sophisticated technology, strict standardization, and appropriate clinical and technical expertise. Second, both studies are essentially descriptive, without providing new insights into mechanisms of disease. Third, age itself influences retinal artery media:lumen ratio, which may be a confounding factor when evaluating structural remodeling of retinal arteries. In fact, retinal vessel effects of blood pressure manifest early in life. In children as young as 6 years, elevated blood pressure was associated with significant retinal arteriolar, but not venular, narrowing.14 Fourth, whereas Harazny et al7 implicate an important role of blood pressure in retinal arterial changes, Cheung et al8 found that retinal narrowing was independent of blood pressure levels. Finally, it should be stressed that the two investigations compared different structural parameters of retinal arteries. In one study media:lumen ratio was measured, whereas in the other arterial narrowing was assessed. Molecular mechanisms contributing to these phenomena may differ.

Data from the studies under discussion are provocative because they pose the question as to whether the retinal vascular changes described are markers of disease or whether they contribute mechanistically to the pathophysiology of hypertension. It is unclear whether retinal vessel remodeling is simply a component of the “classical” hypertensive retinopathy,15 whether it is a marker of target-organ damage,16,17 or whether increased media:lumen ratio in retinal arteries is merely representative of a generalized phenomenon of the microvasculature in hypertension. Moreover, the question arises as to whether noninvasive assessment of retinal artery structure is a feasible and practical approach for clinical evaluation of small vessels in situ and whether such a tool could be included in the battery of “biomarkers” used to predict cardiovascular risk in patients with hypertension and other vascular disorders. It is premature at this stage to advocate such maneuvers but certainly worth pursuing in future studies.

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References
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