A window to vascular remodeling in arterial hypertension

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At the end of the 19th century, hypertensive retinopathy was first described by Markus Gunn in hypertensive patients with renal disease. Nearly 50 years later, Keith and colleagues documented the prognostic value of funduscopic abnormalities in hypertensive patients and categorized hypertensive nephropathy into 4 groups of increasing severity that since then have been taught in medical university schools. In 1966, the ophthalmoscopic changes were confirmed to be predictive of death in patients with essential hypertension.1,2

The usefulness of the classification system and its relevance to current clinical practice, however, have been questioned repeatedly.3 The direct ophthalmoscopic examination has been shown to be unreliable, with high rates of interobserver (20% to 40%) and intraobserver (10% to 33%) variability.4 The criticism refers to stages 1 and 2 of the Keith-Wagner-Barker classification. Only hemorrhages and exudates can be reliably assessed in retinal photographs. A systematic review identified 6 studies that provided data on interobserver agreement for hypertensive retinopathy using retinal photographs.3 In these studies interobserver agreement was modest and fair for focal arterial narrowing and arteriovenous nicking, good for the arteriovenous ratio, and excellent only for hemorrhages and exudates. Most current guidelines for the management of arterial hypertension, therefore, do not recommend fundoscopy as a routine diagnostic test, but advanced retinopathy (hemorrhages, exudates, or papilledema) is accepted as a factor influencing prognosis in hypertensive patients.5

Hypertensive retinopathy is generally considered to be a marker and/or predictor of vascular disease and death. Because the retinal and cerebrovascular circulations share common anatomic, physiological, histological, and embryological features, it is not surprising that hypertensive retinopathy is strongly related to stroke or lacunar infarctions. In a 3-year population-based cohort study with atherosclerotic risk, exudates (cotton-wool spots), retinal hemorrhages, and microaneurysms were associated with a 2-fold to 4-fold higher risk of incident stroke, cognitive decline, white matter lesions, cerebral atrophy, and stroke mortality.1 Signs of microvascular changes (arteriovenous nicking, generalized or focal arteriolar narrowing, and arteriovenous ratio) were weaker but still significantly related to incident stroke. Further population-based longitudinal studies reported consistently that signs of hypertensive retinopathy, in particular, if advanced, were related to a 2-fold to 3-fold increase in the risk of fatal and nonfatal stokes independent of cardiovascular risk factors.1 Inconsistent results were reported for the association of hypertensive retinopathy and coronary heart disease, although an increased risk of coronary events was observed in women but not in men.6 This gender-related observation may reflect the higher risk of coronary microvascular disease among women than in men.

In this issue of Hypertension the relationship between retinal arterial narrowing and myocardial perfusion was analyzed in 234 participants free from clinically diagnosed cardiovascular disease based on self-reported information.7 Myocardial perfusion reserve measured after maximal vasodilation with adenosine reflects microvascular changes in the coronary circulation and may contribute to the risk of coronary heart disease in hypertensive patients independent of obstructive stenosis in epicardial arteries. The major finding of this cross-sectional analysis is that decreased myocardial perfusion reserve was associated with narrower retinal arterioles.7 This association was independent from age, gender, and ethnicity but not from cardiovascular risk factors and was only observed in patients without coronary calcifications. Because macrovascular coronary artery disease was not excluded by coronary angiography, it remains unresolved whether patients with coronary calcification being indicative for epicardial stenosis suffered from coronary macrovascular artery disease. Nevertheless, the study clearly indicates that retinal arterioles that can be examined noninvasively and the coronary microcirculation reveal similar abnormalities at an early stage of vascular injury.

In accordance, microvascular changes of small arteries that were taken from subcutaneous fat tissue were related to coronary flow reserve and predictive of cardiovascular events.8 In essential hypertension, vascular remodeling occurs early in small arteries with a lumen diameter of 100 to 350 μm of which the sizes are similar to the diameter of retinal arterioles. Vascular changes in small arteries may be of a structural (remodeling) or functional (vasoconstriction) nature. In hypertensive patients, endothelium dysfunction has been documented in systemic, coronary, renal, and retinal circulations.9 Structural changes, ie, remodeling of the microvascular wall, lead either to eutrophic (rearrangement of smooth muscle cells, more common in mild-to-moderate hypertension) or hypertrophic remodeling, but both reveal an increased wall:lumen ratio.10 With eutrophic remodeling there is no cell hypertrophy, and vessels have the same...
number of smooth muscle cells, but they are restructured around a smaller vessel lumen and diameter.

Increased wall:lumen ratios of subcutaneous small arteries have been found to predict cardiovascular events in hypertensive patients and in a more heterogeneous cohort including those with secondary hypertension and diabetes.11 Similarly, arteriolar narrowing in the retinal circulation corresponding with the eutrophic remodeling indicates microvascular changes in the coronary circulation3 and predicts cardiovascular mortality.16 However, none of these prospective studies examined or adjusted the results for other indicators of hypertensive organ damage, such as left ventricular hypertrophy, microalbuminuria, intima-media thickness of carotid arteries, or pulse wave velocity. This lack of inclusion of other measures of target organ damage limits the value of evaluating hypertensive retinopathy in hypertension (unless in hypertensive emergency), because the added value is uncertain.3 So far, all of these trials just measured the diameter of the arterioles and/or venules to calculate the arteriovenous ratio. Scanning laser Doppler flowmetry and automatic full-field perfusion imaging analysis enable us now to assess not only the diameter of arterioles but also the wall:lumen ratio increasing the explanatory power of this approach (Figure).12

Vascular injuries to small arteries may occur early in the development of hypertension and may even precede hypertension.10 Narrowing of the retinal arteriolar has been found to predict the risk of hypertension in normotensive subjects and of incident severe hypertension.13 However, the sensitivity of retinal abnormalities associated with hypertension is low (low positive predictive value), and half of the people without hypertensive retinopathy still have hypertension (low negative predictive value). Moreover, only middle-aged and older people were included in the prospective trials, although the association among hypertensive retinopathy, blood pressure, and risk of cardiovascular disease is stronger in younger populations.3 By introducing new tools to assess the remodeling of retinal arterioles noninvasively (ie, wall:lumen ratio), early vascular changes in the retinal circulation can be analyzed more precisely, and limitations and inconsistencies of studies might be resolved.12

Thus, based on our current knowledge, the added value of funduscopy even after introducing photographs and computerized analysis is disappointingly modest. The prospective studies are hampered by the fact that none of the trials have included concurrent measures of hypertensive organ damage. Thus, the precise role and cost-effectiveness calculations of funduscopy cannot be derived. New opportunities to determine vascular changes earlier and more concisely are on the horizon and may offer a new view on the diagnostic and predictive values of hypertensive retinopathy in arterial hypertension.

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References
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