Do microvascular retinal changes improve cardiovascular risk estimation?

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Fundoscopic examination is a unique, noninvasive tool allowing the assessment of retinal vessel changes induced by high blood pressure (BP), which, in turn, may reflect cerebral microangiopathic alterations. Mechanical stretch and increased arteriolar transmural pressure combined with metabolic disorders associated with hypertension cause the release from endothelial cells of neurohormonal factors influencing arteriolar smooth muscle and pericyte tone [1]. Locally activated humoral factors, including angiotensin II, endothelin and insulin, induce arteriolar lumen narrowing, apoptosis of vascular smooth muscle cells and vascular fibrosis. Subtle changes in retinal microcirculation, characterized by increased arteriolar wall-to-lumen ratio and venular dilatation, represent an early stage frequently observed in hypertensive retinopathy. More advanced stages of retinopathy, including the 'exudative stage' (i.e. disruption of the blood–retina barrier, exudation of blood and lipids, retinal ischemia) characterized by microaneurysms, hemorrhages, hard exudates, cotton-wool spots and papilloedema, are fortunately rarely found in current hypertension to day [2].

Since the pioneering study by Keith *et al*. [3], showing a strong association between hypertensive retinopathy and incident mortality, a vast amount of data has been accumulated about the clinical and prognostic value of this condition across different clinical settings and ethnicities. In the observational survey by Keith *et al*. [3], including 219 hypertensive patients, the authors reported a dramatic decline in survival during a 5-year follow-up period from grade 1 to 4 retinopathy. All-cause mortality rate was strongly related to retinopathy, increasing from 30% in grade 1, to 46% in grade 2, 80% in grade 3, up to 99% in grade 4. In the decades from 1950 through 1980, several reports confirmed the association of hypertensive retinal vascular damage with excess cardiovascular morbidity, in particular with stroke [4,5]. These findings, however, have a limited application to contemporary clinical practice, due to a number of limitations. First, retinal alterations were simply defined by fundoscopic examination, a method affected by poor intraobserver and interobserver reproducibility. Second, in older studies, more advanced degrees of retinopathy, including hemorrhages and exudates, were observed in the majority of patients. However, focal or generalized arteriolar narrowing and arteriovenous crossing are the most prevalent retinal alterations observed in contemporary hypertension, more frequently detected than other markers of organ damage with proven prognostic value (i.e. left ventricular hypertrophy, carotid intima–media thickening or plaques and microalbuminuria). Moreover, the prognostic value of these retinal alterations has been questioned by several cross-sectional studies [6,7]. Thus, the 2007 European Society of Hypertension-European Society of Cardiology guidelines stated that examination of eye grounds is only recommended in patients with severe hypertension, in whom hemorrhagic and exudative lesions and papilloedema are most likely found, whereas milder retinal changes are largely aspecific in middle-aged and elderly individuals [8]. A reappraisal of this position, however, is needed on the light of new evidence coming from recent studies.

In a large population-based Japanese study, including 87 890 individuals (29 917 men and 57 973 women, age range 40–79 years) who completed an annual health check-up, Sairenchi *et al*. [9] examined whether mild hypertensive retinopathy, assessed by nonmydriatic retinal photography graded by the Keith–Wagener–Barker classification, was a risk factor for cardiovascular mortality. The presence of mild (grade 1 and 2) retinopathy, initially diagnosed in 7473 men (25%) and 12 152 women (21%), was found to be independently related with an increased risk of death from cardiovascular disease during an average 14-year follow-up period, the hazard ratios for grade 1 and 2 retinopathy being, respectively, 1.24 [95% confidence interval (CI) 1.12–1.28] and 1.23 (95% CI 1.03–1.47) among men, 1.12 (95% CI 1.01–1.24) and 1.44 (95% CI 1.24–1.68) among women. This study, the largest targeting the prognostic value of hypertensive retinopathy, extends previous evidence of an association of moderate–severe retinal

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damage with incident cardiovascular disease to milder degrees of retinopathy.

Furthermore, in the last few years, selective methods for a more objective assessment of retinal damage in hypertension have developed [10]. *In vivo*, vascular changes can be detected by different approaches aimed at measuring parameters such arteriolar outer diameter, lumen diameter, wall-to-lumen ratio, cross-sectional area and retinal capillary flow [11]. Recent advances in retinal photographic techniques and computer-assisted image analysis have provided the opportunity to quantify subtle abnormalities in retinal vasculature. Cross-sectional diameter of retinal arterioles and venules, indeed, is presently measured by validated semi-automated programs and averaged to obtain a representative value of vessels in the region between one and a half disc diameter from the optic disc margin. This method has been shown to have a high intraobserver and interobserver reliability (weighted kappa >0.80 for intraobserver and >0.85 for interobserver reproducibility) [12].

Several prospective studies performed worldwide have demonstrated associations of retinal microvascular changes with incident cardiovascular outcomes supporting the view that retinal vessel caliber may become a novel marker of cardiovascular risk. These studies have shown that arteriolar narrowing may precede the development of clinical hypertension [13,14] and predict nonfatal and fatal coronary events, particularly in women. Interestingly, increased venular caliber has been found to be an independent predictor of coronary artery disease and stroke in both sexes [15–17]. Recently, in a cross-sectional observational study including 1988 participants aged 49–97 years, retinal venular dilatation was associated with a significant cognitive impairment (odds ratio = 1.8, 95% CI 1.0–3.2), suggesting that increments in venular caliber may reflect a cognitive deterioration [18]. Moreover, the Atherosclerosis Risk in Communities Study reported that retinal microaneurysms, arteriovenous nicking and hemorrhages but not arteriolar and venular caliber were associated with a 10-year incident cerebral atrophy as assessed by ventricular enlargement at magnetic resonance [19].

NEW INSIGHTS AND PERSPECTIVES FROM THE STUDY BY GARCIA-ORTIZ *ET AL.*

In the current issue of the *Journal of Hypertension*, Garcia-Ortiz *et al.* [20] report the findings of a cross-sectional study aimed at evaluating the reliability of semi-automated measurements of retinal vessel caliber as well as the relationship of these measurements with validated markers of organ damage such as left ventricular hypertrophy, carotid intima-thickness, pulse wave velocity, microalbuminuria, glomerular filtration rate and estimates of cardiovascular risk based on the Framingham score. For this purpose, the authors investigated 110 untreated and treated hypertensive patients, 55 diabetic patients and 45 healthy individuals, aged 34–75 years, free of overt cardiovascular disease, referred to a primary care clinics. All participants underwent bilateral retinography, without previous mydriasis; all examinations were performed outside the ophthalmologic setting. The external caliber of arterioles and venules in the upper and lower temporal quadrants was measured and arteriole/venule index was calculated by a software automatically recognizing the vessels and providing an average estimate in μm on the basis of multiple measurements performed within a few minutes. By this semi-automatic quantitative approach the intraobserver and interobserver reproducibility of vessel diameter assessment was even better than that provided by previous large-scale studies carried out in ophthalmology units [8]. For example, the mean difference between two observers ranged from 0.22 μm for the left arteriolar caliber (106.37 vs. 106.14 μm) to 1.45 μm for the right venular caliber (139.61 vs. 138.16 μm) with an overall variability lower than 1%. From these data, three considerations can be drawn. First, advances in fundus photography and new softwares improve the accuracy in the assessment of retinal vessels diameter. Second, new imaging techniques, now available outside the specialist ophthalmology setting, may offer the opportunity to extend the screening of retinal abnormalities in routine clinical practice. Third, the short time required for the analysis of each patient (approximately 2 min for both eyes) represents a real advantage over the time-consuming and expensive ultrasound techniques currently adopted for the assessment of subclinical cardiac and vascular alterations.

In their investigation, Garcia-Ortiz *et al.* [20] were able to demonstrate an independent association between arteriovenular ratio (AVR), venular caliber, but not the arteriolar one, with Framingham score and microalbuminuria. According to multivariate analyses, the strength of association of venular caliber with Framingham score and microalbuminuria was stronger than that found for AVR; the association with this last parameter, indeed, lost the statistical significance after adjustment for sex. These findings suggest that venular caliber is more accurate than the arteriolar one in reflecting cardiovascular risk and endothelial dysfunction, as expressed by Framingham algorithm and microalbuminuria, respectively, and AVR is reduced not only by arteriolar vasoconstriction or remodeling but also by important increments in venular diameter, as shown in the present study.

The link between venular dilatation and cardiovascular risk as well as organ damage is not unexpected. Recent studies, indeed, indicate that venular diameter is increased in a variety of pathologic conditions characterized by sustained endothelial dysfunction, such as hypertension, metabolic syndrome, diabetes, atherosclerosis, dyslipidemia and inflammation. Compatible with these observations is the view that venular retinal network is not only a conductance system but also an active player in the control of eye microcirculation [1,21].

Some further aspects of the study by Garcia-Ortiz *et al.* [20] deserve a mention. At difference from some previous reports but in accordance with others, their study showed no significant relationship between retinal arteriolar diameter and carotid atherosclerosis, pulse wave velocity and left ventricular hypertrophy as assessed by electrocardiographic criteria. The small study sample may explain this result. A more reliable assessment of cardiac involvement by echocardiography may have yielded different results. As approximately half of the patients were on

antihypertensive treatment, this may have altered the relationship between retinal caliber and organ damage.

Although the present study shows that retinal vascular imaging is markedly improved in terms of feasibility and reliability and provides useful information to clinicians in the assessment of cardiovascular risk, further work is needed before translating these findings into clinical practice. Normal reference values of retinal parameters specific for age, sex and ethnicity and, more importantly, the prognostic value of microvascular alterations compared with conventional risk factors should be the target of future research.

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Conflicts of interest

The authors report no conflicts of interest.

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