Editorial Comment

Do microvascular retinal changes improve cardiovascular risk estimation?

Cesare Cuspidi and Carla Sala

F undoscopic 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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*Department of Clinical Medicine and Prevention, University of Milano-Bicocca, **Istituto Auxologico Italiano IRCCS, *Heart and Lung Department, University of Milano and *Fondazione Ospedale Maggiore Policlinico, Milan, Italy

Correspondence to Professor Cesare Cuspidi, Clinical Research Unit, Istituto Auxologico Italiano, Viale della Resistenza 23, 20036 Meda, Italy. Tel: +39 0362 772433; fax: +39 0362 772416; e-mail: cesare.cuspidi@unimib.it


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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 hyperten-
sion 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 capil-
lar 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 intra-
observer 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 arterio-
lar 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 cogni-
tive 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 micro-
aneurysms, 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, microalbu-
minuria, glomerular filtration rate and estimates of cardio-
vascular 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 pro-
viding 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 assess-
ment 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 (approxim-
ately 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 arterio-
venular ratio (AVR), venular caliber, but not the arteriolar
one, with Framingham score and microalbuminuria.
According to multivariate analyses, the strength of associ-
ation of venular caliber with Framingham score and micro-
albuminuria was stronger than that found for AVR; the
association with this last parameter, indeed, lost the stat-
istical significance after adjustment for sex. These findings
suggest that venular caliber is more accurate than the
arteriolar one in reflecting cardiovascular risk and endo-
thelial 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, dyslipide-
mia 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 electro-
cardiographic criteria. The small study sample may explain
this result. A more reliable assessment of cardiac involve-
ment by echocardiography may have yielded different
results. As approximately half of the patients were on
anthypertensive 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

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REFERENCES