The Optic Fundus and Retinal Circulation: New Technology for an Old Examination

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13.1 Introduction

As the cornea, lens, and vitreous humor lack blood vessels and are transparent, the retina offers the unique opportunity to examine the body's microvasculature in vivo safely, repeatedly, and noninvasively. Retinal arterioles undergo similar changes as cerebral, coronary, and peripheral arterioles in hypertension indicating that retinal arteriolar abnormalities mirror structural and functional microvascular changes elsewhere in end-organ tissues [1, 2]. As retinal and cerebral circulation share common anatomical, physiological, and embryological features, retinal circulation might be a model for cerebral microvasculature. This was supported by an autopsy study of patients with stroke, which showed a close correlation between retinal and cerebral arteriolar findings [3]. Therefore, it is not surprising that retinal microvascular abnormalities present an important prognostic value, in particular with respect to cardiovascular events and cardiovascular mortality [4].

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure lists retinopathy as one of several markers of target organ damage in hypertension [5]. In contrast, the current guidelines of the European Society of Hypertension and European Society of Cardiology 2007/2009 [6, 7] list retinopathy as target organ damage only for grades 3 and 4 of hypertensive retinopathy. This change in guidelines reflects the repeated criticism that arose over the last decade with respect to the usefulness of the traditional classification system of hypertensive retinopathy for current clinical

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practice [8–10]. As a result, much research effort has been focused on the development of new imaging techniques to analyze retinal arteriolar structure and function in subjects with hypertension more precisely.

13.2 Historical Context and Classification

Signs of hypertensive retinopathy were already described by Liebreich [11] in 1859 and then by Gunn [12] in 1892. The traditional classification of hypertensive retinopathy can be dated to a publication by Keith and colleagues in 1939 in which the authors classified hypertensive retinopathy into four grades of increasing severity [13]. In the last 20 years, retinal photographs were repeatedly used to assess the retinal microvasculature in patients with arterial hypertension. Further progress in imaging techniques [digital photography and scanning laser Doppler flowmetry (SLDF)] now allows the assessment of early structural [e.g., arteriole-to-venule ratio (AVR)] of retinal vessels, arteriolar length-to-diameter ratio, vessel density/rarefaction and tortuosity, the wall-to-lumen ratio of retinal arterioles and early functional parameters (e.g., vasoconstrictor and vasodilatory properties) of retinal microvasculature in arterial hypertension.

13.3 Assessment of Hypertensive Retinopathy

13.3.1 Hypertensive Retinopathy by Ophthalmoscopy

Direct ophthalmoscopy provides a magnified (x16) vision of the posterior pole of the retina. The procedure ought to be performed after the induction of pharmacological mydriasis and requires a certain degree of patient collaboration. It is an inexpensive method to assess retinal arteriolar structure. However, direct ophthalmoscopy has been shown to be subjective and unreliable [14–16], with significant interobserver (20–42 %) and intraobserver (10–33 %) variations in the assessment of different retinal lesions [16]. Moreover, it was found to be particularly unreliable in mild to moderate hypertension [15].

Test–retest analyses revealed poor reliability in the early stages of hypertensive retinopathy, whereas grade 3 and 4 retinopathy as classified by Keith and colleagues [13] is still a valid diagnostic criteria of severe retinal damage [4, 17–19]. In 2004, Wong and Mitchell proposed a new and simple classification system of retinal microvascular signs, detectable by ophthalmoscopy, based on the strength of the reported associations of various retinopathy markers [8]. They graded retinal vascular signs into mild [generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, and arteriolar wall opacity (silver wiring)], moderate [hemorrhage (blot-, dot-, or flame-shaped), microaneurysm, cotton-wool spot and hard exudates], and malignant (moderate retinopathy plus optic disc swelling) [8].

13.3.2 Hypertensive Retinopathy by Retinal Photography

The use of retinal photographs in combination with standardized protocols, blinded grading, and special software has improved the reliability of assessing retinal microvascular abnormalities and has led to a more precise and objective quantification of retinal microvascular signs [20]. Retinal photography can be carried using standard film or with digital equipment. Both traditional fundus cameras and *nonmydriatic* models are widely used.

13.3.2.1 Arteriole-to-Venule Ratio

Digital nonmydriatic cameras allow computer-assisted or fully automated detection of different retinopathy lesions, and the calculation of the AVR of retinal vessels. The calculation of the AVR is of particular interest since the measurement of arteriolar narrowing cannot be quantified by ophthalmoscopy. The calculation of the AVR is based on the assumption that high blood pressure is associated with narrower retinal arteriolar diameters [21–24], though it does not affect retinal venular diameters. However, recent data suggest that venular diameter is also affected by several conditions including diabetes, metabolic syndrome, smoking, and inflammation [25–29], and therefore influence the AVR independently from changes in the diameter of retinal arterioles. Nonetheless, the narrowing of arterioles is considered to represent the earliest alteration of the microvasculature, including the retinal microvasculature, in hypertensive subjects [30–32].

13.3.2.2 Topological Changes in Retinal Vascular Architecture

The parameters of the arteriolar and venular network may also be altered in patients with primary hypertension. Several parameters have been suggested to assess arteriolar narrowing (e.g., the length-to-diameter ratio) calculated as the ratio of the length of a vessel segment between two branching points to its average diameter), vascular rarefaction (e.g., the number of terminal branches), or vessel tortuosity (e.g., the ratio of the actual length of the vessel segment to the straight line distance between two connected branching points) [33, 34]. However, these parameters, although scientifically very interesting, are as yet to be introduced into clinical practice.

13.3.3 Hypertensive Retinopathy by Scanning Laser Doppler Flowmetry

SLDF with automatic full-field perfusion imaging analysis (AFFPIA) allows the measurement of retinal capillary perfusion as well as the calculation of the inner and outer diameters of retinal arterioles, thereby allowing the precise analysis of retinal vascular function and arteriolar remodeling in hypertension [35–37]. Of clinical interest, both vascular dysfunction—at least when assessed in the peripheral [38, 39] and coronary [40] circulation—and arterial remodeling—at least when assessed in

vitro in small subcutaneous arteries and arterioles [41–43]—have been found to be of prognostic significance with respect to cardiovascular events.

SLDF with AFFPIA is performed without the need for prior mydriasis. The method is safe, noninvasive, and has a short examination time of approximately 5 min. It is highly reliable [36, 44–46], but must be performed by a trained and certified observer.

13.3.4 Vascular Function of Retinal Vessels

Retinal vascular function can be assessed by examining the vasodilator capacity of retinal vessels, i.e., the increase in retinal capillary perfusion in response to flicker light exposure [37, 47–49], or more invasively, by examining the vasoconstrictor properties of retinal vessels by assessing the decrease in retinal capillary perfusion in response to the infusion of the nitric oxide synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) [35, 37, 48, 49].

Recent studies have shown that the vasoconstrictor response of retinal vessels, assessed by the change in retinal capillary blood flow in response to the infusion of L-NMMA, is impaired in lean [35] and obese or overweight [37] subjects with primary hypertension. Blood pressure reduction induced pharmacologically by inhibitors of the renin–angiotensin system was found to improve the vasoconstrictor response of retinal vessels to L-NMMA infusion [35].

13.3.5 Remodeling of Retinal Arterioles

Remodeling of retinal arterioles is assessed by measuring the inner retinal arteriolar diameter in perfusion images and the outer retinal arteriolar diameter in reflection images, with subsequent calculation of the wall-to-lumen ratio [36, 37, 50, 51], wall cross-sectional area [37, 50, 51], and other parameters of retinal arteriolar remodeling according to previously described formulas [50, 51] (see Fig. 13.1).

The wall-to-lumen ratio of retinal arterioles was found to be greater in hypertensive compared to normotensive patients and systolic and diastolic blood pressure levels were found to be related to the wall-to-lumen ratio of retinal arterioles [37]. Treated hypertensive patients with well-controlled hypertension revealed lower wall-to-lumen ratio of retinal arterioles than patients with uncontrolled hypertension [36]. Moreover, in hypertensive patients, the wall-to-lumen ratio of retinal arterioles was negatively related to the vasodilatory response of retinal vessels to flicker light exposure, indicating that hypertensive patients with a greater wall-to-lumen ratio might reveal impaired vasodilatory properties of their retinal vessels [48].
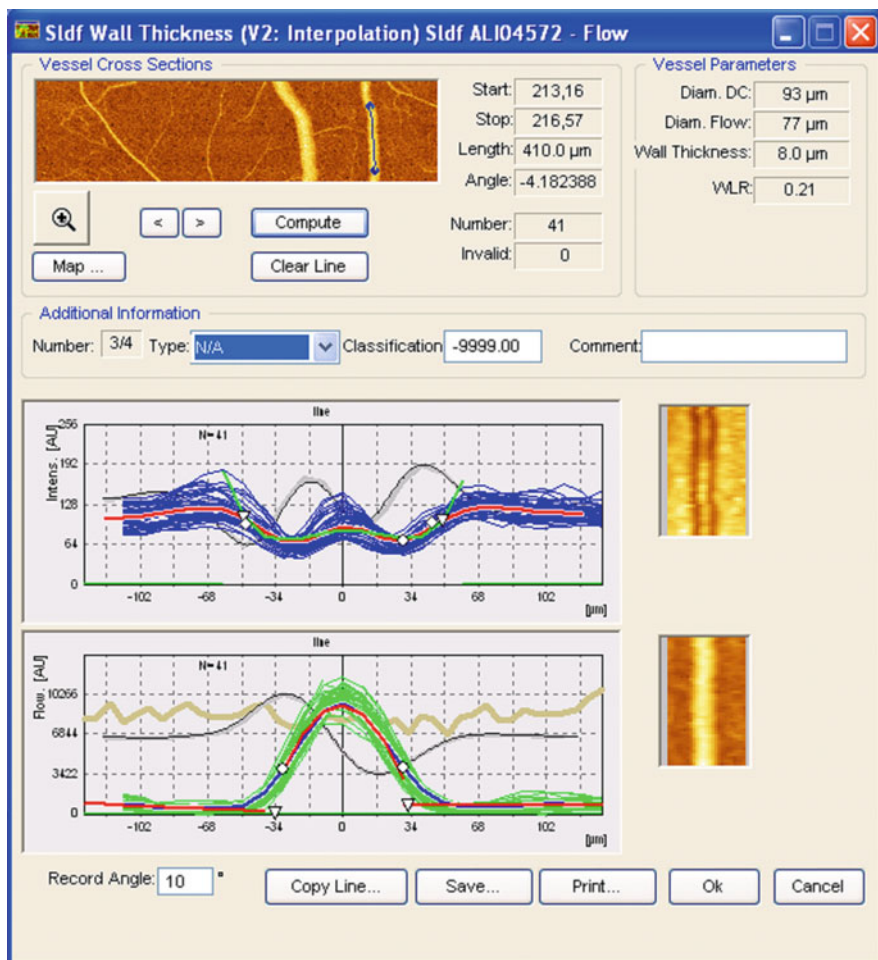
Fig. 13.1 Screenshot for the assessment of remodeling of retinal arterioles using scanning laser Doppler flowmetry with automatic full-field perfusion imaging analysis. The outer diameter is measured in reflexion images, whereby differences between the light intensity of reflected light between two points lying side by side, due to the acute angle at the outer vessel wall border, allow the detection of the outer diameter of the arteriole. The inner diameter is measured in perfusion images, whereby the bloodstream, due to high velocity in the center of the arteriolar lumen, and decreasing blood velocity toward to periphery of the arteriolar lumen allow the calculation of a parabolic velocity curve and thereby the measurement of the inner diameter of the arteriolar vessel. Subsequently, the wall-to-lumen ratio, wall cross-sectional area, and wall thickness can be calculated based on the measurements of the inner and outer diameter of the arteriole [37]

13.4 Retinal Microvascular Abnormalities and Hypertensive Organ Damage

13.4.1 Cerebrovascular Disease

The Atherosclerosis Risk in Communities (ARIC) study [17], the Cardiovascular Health Study [18], the Beaver Dam Eye Study [4], and the Shibata Study [19] revealed an increased risk of stroke in patients with hypertensive retinopathy, analysed by retinal photographs, than in patients without signs of hypertensive retinopathy. However, these population-based studies also indicate that earlier signs of hypertensive retinopathy (e.g., generalized and focal narrowing of arterioles and arteriovenous nicking) were weaker and less consistent when associated with stroke [17] and death from stroke [4]. The ARIC study demonstrated that hypertensive retinopathy adds additional predictive value for incident stroke in patients with cerebral white matter lesions [52]. Retinal microvascular alterations were also associated with magnetic resonance imaging-defined subclinical cerebral infarction [53], cerebral white matter lesions [52], cognitive impairment [54, 55], dementia [55], and cerebral atrophy [56]. The wall-to-lumen ratio [36] and wall cross-sectional area [57] of retinal arterioles have been found to be greater in hypertensive subjects with a history of a cerebrovascular event compared with uncomplicated hypertensive and normotensive subjects.

13.4.2 Cardiac Disease

Retinal microvascular abnormalities have been found to be associated with ischemic changes on electrocardiography [58], left ventricular hypertrophy [59], coronary heart disease [60–63], congestive heart failure [64], and lower hyperemic myocardial blood flow and perfusion reserve in subjects without coronary artery calcification [65].

13.4.3 Renal Disease

In the ARIC study, subjects with retinopathy were more likely to develop renal dysfunction than individuals without [66]. This was confirmed by the Cardiovascular Health Study [67]. In a cross-sectional study, we found a close relationship between the wall-to-lumen ratio of retinal arterioles and urinary albumin excretion, and an estimated creatinine clearance >60 mL/min in 37 male subjects who were either normotensive or revealed primary hypertension [68].

13.5 Arterial Stiffness, Carotid Intima-Media Thickness, and Carotid Plaques

In the ARIC study, carotid arterial stiffness, estimated from high-resolution ultrasonic echo tracking of the left common carotid artery and defined as the adjusted arterial diameter change, was related to generalized retinal arteriolar narrowing, as assessed by examining the AVR of retinal vessels in subjects aged 45–64 [69]. In the Multi-Ethnic Study of Atherosclerosis, reduced aortic distensibility, as an indicator for aortic stiffness, was associated with reduced arteriolar caliber in participants free of cardiovascular disease [70]. In a small study in patients with primary hypertension, retinopathy was associated with carotid intima-media thickness and carotid plaque score [71].

All these trials clearly indicate a coincidental occurrence of microvascular retinal abnormalities and cardiovascular morbidity and hypertensive target organ damage, respectively. However, although some of these studies adjusted for other classic cardiovascular risk factors to a greater or lesser extent, none of them adequately evaluated whether the assessment of microvascular retinal changes is of additive value on top of the assessment of established parameters of target organ damage [6] (e.g., urinary albumin excretion, left ventricular hypertrophy, carotid artery intima-media thickness, and pulse wave velocity). This lack of inclusion of other measures of target organ damage limits the value of evaluating retinopathy in hypertension (unless in hypertensive emergency). Nonetheless, with the advancement of imaging technologies, changes in retinal microvascular circulation may be detected noninvasively at an early stage and more accurately than other subclinical target organ damage.

13.6 Retinal Microvascular Alterations and Mortality

Several studies performed in the middle of the 20th century or thereafter, which relied on ophthalmoscopy (with all its limitations), revealed that hypertensive patients with moderate to severe retinal microvascular abnormalities had an increased risk of mortality [13, 58, 72–78]. However, it can be problematic to generalize from these earlier studies, carried out in patients with uncontrolled and untreated hypertension to current patients with cardioprotective treatment, who present with less severe signs of hypertensive retinopathy.

In a nested case–control analysis of the Beaver Dam Eye Study, an increased risk of ischemic heart disease death was associated with a suboptimal relationship of retinal arteriolar diameter at bifurcation, even after adjusting for age, sex, past history of cardiovascular disease, and other known cardiovascular risk factors [79]. In another nested case–control analysis of the Beaver Dam Eye Study, a weak association between generalized retinal arteriolar narrowing, defined by the AVR of retinal vessels, and cardiovascular mortality was found for subjects aged 43–74 but not for subjects aged 75 years or older [4], whereas an analysis of the entire

Beaver Dam cohort did not reveal an association between the AVR of retinal vessels or its components (arteriolar and venular diameter) and all-cause or vascular disease-related mortality [80]. However, adjustment for other parameters of hypertensive target organ damage was not performed in the aforementioned studies.

Unfortunately, studies analyzing the impact of retinal vascular function (i.e., the change of retinal capillary blood flow in response to flicker light exposure or to an infusion of L-NMMA) and/or precise analyses of retinal arteriolar remodeling (i.e., the calculation of the wall-to-lumen ratio and wall cross-sectional area of retinal arterioles) on cardiovascular mortality have not been conducted as these methodical approaches have only recently been introduced [35, 36].

13.7 Conclusions

There is an abundance of evidence that advanced retinopathy [grade 3 and 4 hypertensive retinopathy or moderate to severe (malignant) retinopathy] implies an increased risk of cardiovascular complications and mortality in hypertensive subjects. However, the evidence is weaker and inconsistent for the earlier signs of hypertensive retinopathy. Earlier signs of hypertensive retinopathy are very common among hypertensive subjects and appear to be among the earliest signs of vascular alterations in hypertension. Unfortunately, the detection of early retinopathy in hypertension is currently associated with several limitations.

First, direct ophthalmoscopy is subjective and unreliable in patients with grade 1 and 2 hypertensive retinopathy. Second, grade 1 and 2 hypertensive retinopathy cannot be distinguished by most physicians, even when retinal photographs are analyzed. Third, the approach of calculating the AVR of retinal vessels, as a parameter of generalized retinal arteriolar narrowing, from digitized photographs has insufficient explanatory power since AVR is not only dependent on the arteriolar diameter but also on the venular diameter. However, a novel approach, SLDF with AFFPIA, might be useful in better characterizing early retinal microvascular alterations, since this method allows the detection of retinal vascular function and the detailed analysis of retinal arteriolar remodeling. Future studies with large cohorts that also adjust for other markers of target organ damage and cardiovascular risk factors are needed to assess the impact of retinal vascular function and arteriolar remodeling on clinical cardiovascular disease as well as mortality.

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