Retinal Circulation in Arterial Disease

28

Christian Ott and Roland E. Schmieder

Hypertension has profound effect on the structure and function of the eye. In this chapter, we will focus on hypertensive retinopathy. Only for the sake of completeness, it should be mentioned that hypertension-related changes also include hypertensive optic neuropathy and hypertensive choroidopathy. Moreover, there are ocular diseases where hypertension is a potential risk factor, e.g., age-related macular degeneration and glaucoma. Most importantly, hypertension causes structural and functional vascular changes. We elaborate on the current knowledge of these processes, including innovative findings related to new applied technologies.

28.1 Vascular Remodeling

Since the pathophysiological concept of vascular remodeling was in detail described in Chap. 5, only few words will be mentioned. Remodeling can be of two types – eutrophic and hypertrophic, but both types result in an increase in the media-to-lumen ratio of small arterioles. In eutrophic remodeling, both the outer and the lumen diameter are reduced, but the media cross-sectional area is not increased because the increase in the wall thickness-to-lumen diameter ratio is caused by a rearrangement of the smooth muscle cells around a narrowed lumen [1]. In contrast, in hypertrophic remodeling, an enhanced growth response resulting in an increased media cross-sectional area was documented. Eutrophic remodeling predominates in patients with essential hypertension, and hypertrophic remodeling was found in patients with severe and long-standing hypertension.

C. Ott • R.E. Schmieder (✉)
Department of Nephrology and Hypertension, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Ulmenweg 18, Erlangen 91054, Germany
e-mail: christian.ott@uk-erlangen.de; roland.schmieder@uk-erlangen.de

© Springer International Publishing Switzerland 2015

A. Berbari, G. Mancia (eds.), *Arterial Disorders: Definition, Clinical Manifestations, Mechanisms and Therapeutic Approaches*,
DOI 10.1007/978-3-319-14556-3_28

Table 28.1 Traditional Keith-Wagener-Barker classification and simplified (Wong-Mitchell) classification

Keith-Wagener-Barker classification		Simplified (Wong-Mitchell) classification	
Grade	Features	Grade	Features
1	Mild generalized retinal arteriolar narrowing	None	No detectable signs
2	Definite focal narrowing and arteriovenous nipping	Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity ("copper wiring") of arteriolar wall or a combination of these signs
3	Signs of grade 2 retinopathy plus retinal hemorrhages, exudates, and cotton wool spots	Moderate	Retinal hemorrhages (blot, dot, or flame-shaped), microaneurysm, cotton wool spot, hard exudates, or a combination of these signs
4	Severe grade 3 retinopathy plus papilledema	Malignant	Signs of moderate retinopathy plus swelling of the optic disk

The importance of vascular remodeling is based on a finding that it is one of the early (or even the earliest) processes that occurs in response to increased blood pressure (BP) and leads to hypertensive end-organ damage [2], but also that effective antihypertensive treatment is capable to reverse these vascular adaptive processes [3].

The exceptional position of retinal vasculature is known for a long time. Already in 1939, Keith et al. has stated "because the arterioles are small and are difficult to visualize in the peripheral organs, for example, in the skin, mucous membranes, and voluntary muscle, the retina, as seen through the ophthalmoscope, offers a unique opportunity for observing these small vessels from time to time. Therefore, we think that certain visible changes of the retinal arterioles have been of exceptional value in affording a clearer clinical conception of altered arteriolar function throughout the body." [4]. Based on the pioneering work of Keith, Wagener and Barker, their four-group grading system with increasing severity (Table 28.1) was widely applied in the last decades for the stratification of risk in hypertensive patients [4]. However, the clinical usefulness, and hence relevance to current clinical practice, has been questioned, because of poor reproducibility (e.g., 20–40 % interobserver variability) and weak association with other target organ damage (TOD) in grade I and II retinopathy, respectively [5].

Subsequently, a simplified three-grade classification system according to the severity of the retinal signs was proposed by Wong and Mitchell [6] (Table 28.1, Fig. 28.1), based on the evidence that certain hypertensive retinopathy signs (e.g., arteriolar narrowing or arteriovenous nicking) are independently associated with cardiovascular (CV) risk. In a small study comprising 50 normal and 50 hypertensive fundi, respectively, inter- and intraobserver reliabilities of the simplified three-grade classification system and the traditional four-grade classification system introduced by Keith, Wagener and Barker were reported to be comparable [7].

In the ESH/ESC guidelines, it is no longer recommended in general [8]. However, the retinal circulation offers the unique opportunity to visualize repeatedly the

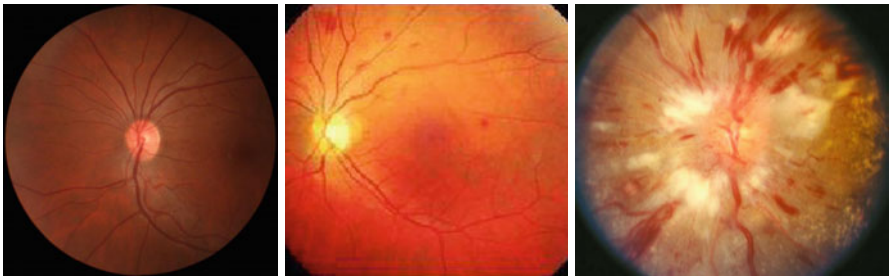

Fig. 28.1 Funduscopy (grade none, moderate, and malignant)

body's microcirculation directly, noninvasively, and safely in vivo. Hence, in the last decade, new and more specific approaches were introduced to overcome these shortcomings and to detect reliable early changes of the retinal circulation.

28.2 Retinal Photographs/Funduscopy (Static)

In the last two decades, several large-scale, population-based studies assessing retinal photographs were conducted, including patients with and without hypertension. In (most of) these studies, standardized protocols of retinal photographs (45° nonstereoscopic color retinal photograph centered between the optic disk and the macula) were used to define specific signs of retinopathy, but not regarding a prespecified grading system. In part, retinal abnormalities were described based solely on qualitative parameters, such as tortuosity, arteriovenous crossing, caliber, and optic disk, but due to limited clinical usefulness, these data will not be reviewed. As further improvement, the imaging software "Interactive Vessels Analysis" (IVAN) (University of Wisconsin, Madison, WI, USA) has been established. This system conducts semiautomated measurement of retinal arterioles and venules, and hence its ratio (A/V ratio); however, it is not able to evaluate the retinal vascular wall directly.

Based on this approach, these studies have analyzed the relationship between retinal vascular alterations and their association with BP, TOD, and CV events which are (in part) summarized in Table 28.2.

It has been repeatedly shown that retinal alterations are strongly correlated with past, current, and incident hypertension. In most of these large-scale studies, associations with directly assessed (generalized) arteriolar narrowing or a decreased A/V ratio, indirectly indicative of proposed arteriolar narrowing, and hypertension were reported (for details, see Table 28.2). In contrast, conflicting results according to retinal venules and hypertension were found. For example, in the Blue Mountains Eye Study, venular narrowing was associated with current hypertension [19]. In accordance, in the Rotterdam Study, venular narrowing was found to be predictive of current and incident blood pressure [28], but in the Multi-Ethnic Study of

Table 28.2 Large scale, population-based studies (in alphabetical order) assessing associations between retinal vascular caliber (based on retinal photography) and blood pressure, target organ damage, and cardiovascular risk (in chronological order)

Study	Country	Ethnicity	Year	Sample size	Retinal vascular	Finding
Atherosclerosis Risk In Communities Study (ARIC)	USA	White, black	1999	9,300	A/V ratio	Past and current blood pressure [9]
			2001	10,358	A/V ratio	Incident stroke [10]
			2002	9,648	A/V ratio	Incident CHD, acute MI (only in women) [11]
			2004	5,628	A/V ratio	Incident hypertension [12]
		(Only) black	2008	1,439	Generalized arteriolar narrowing	Left ventricular hypertrophy [13]
					A/V ratio	Left ventricular hypertrophy [13]
		White, black	2010	10,496	Generalized arteriolar narrowing	Incident lacunar stroke [14]
					Generalized venular widening	Incident lacunar stroke [14]
Beaver Dam Eye Study (BDES)	USA	White	2003	1,611	A/V ratio	CV mortality (43–74 years) [15]
			2003	4,926	Retinal arteriolar diameter	Current blood pressure [16]
					A/V ratio	Current blood pressure [16]
			2004	2,451	A/V ratio	Incident hypertension [17]
			2007	4,926	Smaller arterioles	CHD death [18]
					Larger venules	CHD death [18]

Study	Country	Ethnicity	Year	Sample size	Retinal vascular	Finding
Blue Mountains Eye Study (BMES)	Australia	White	2003	3,654	Arteriolar narrowing	Current blood pressure [19]
					Venular narrowing	Current blood pressure [19]
					A/V ratio	Current blood pressure [19]
			2004	2,335	Arteriolar narrowing	Past and current systolic/diastolic blood pressure [20]
					AV ratio	Past diastolic and current systolic/diastolic blood pressure [20]
			2004	1,319	Arteriolar narrowing	Incident severe hypertension [21]
					A/V ratio	Incident severe hypertension [21]
			2006	3,654	Venular caliber increase	CHD death (men and women, 49–75 years) [22]
					Arteriolar caliber decrease	CHD death (women, 49–75 years) [22]
					A/V ratio	CHD death (women, 49–75 years) [22]
Cardiovascular Health Study (CHS)	USA	White, black	2002	2,405	Arteriolar narrowing	Past and current blood pressure [23]
					A/V ratio	Current blood pressure [23]
			2006	1,992	Smaller arteriolar caliber	Incident CHD [24]
					Larger venular caliber	Incident CHD and stroke [24]
					A/V ratio	Incident CHD [24]
Multi-Ethnic Study of Atherosclerosis (MESA)	USA	White, Hispanics, Black, Chinese	2006	5,979	Smaller arteriolar caliber	Current blood pressure [25]
			2009	2,583	Narrower arteriolar diameter	Incident hypertension [26]
					Wider venular diameter	Incident hypertension [26]
			2011	4,594	Arteriolar narrowing	Incident CKD stage 3 (only whites) [27]

(continued)

Table 28.2 (continued)

Study	Country	Ethnicity	Year	Sample size	Retinal vascular	Finding
Rotterdam Study	Netherlands	White	2004	5,674	Arteriolar diameter decrease	Current blood pressure [28]
					Venular diameter decrease	Current blood pressure [28]
					A/V ratio	Current blood pressure [28]
			2006	1,900	Arteriolar narrowing	Incident hypertension [29]
					Venular narrowing	Incident hypertension [29]
					A/V ratio	Incident hypertension [29]
			2006	5,540	Larger venular diameter	Incident stroke, cerebral infarction [30]
			2010	5,518	Larger venular caliber	Incident stroke, cerebral infarction, intracerebral hemorrhage [31]
Singapore Malay Eye Study (SiMES)	Singapore	Malay	2008	3,019	Smaller arteriolar caliber	Current blood pressure [32]
			2009	2,581	Arteriolar narrowing	Prevalent CKD, micro-/ macroalbuminuria [33]
Singapore Prospective Study Program (SP2)	Singapore	Chinese, Malay, Indian	2009	3,749	Arteriolar caliber decrease	Current blood pressure [34]
					Venular caliber increase	Current blood pressure [34]
					A/V ratio	Current blood pressure [34]
			2009	3,602	Arteriolar caliber decrease	Prevalent CKD [35]
Sydney Childhood Eye Study	Australia	White, Chinese, and others	2007	1,572	Arteriolar narrowing	Current blood pressure [36]

Atherosclerosis, venular widening was associated with incident hypertension [26]. While arteriolar narrowing can easily be harmonized with hypertension, it may be more difficult to explain why wider retinal venular caliber is associated with development of hypertension. A recent meta-analysis, comprising 10,229 patients without prevalent hypertension, diabetes, or CV disease, proposed that 2,599 patients developed new-onset hypertension during follow-up of 2.9–10 years. Both arteriolar narrowing (OR per 20 μm difference 1.29, 95 % CI 1.20–1.39) and venular widening (OR per 20 μm difference 1.14, 95 % CI 1.06–1.23) were independently associated with incident hypertension [37].

Importantly, in a population-based cohort comprising 1,572 children aged 6–8 years, each 10 mmHg increase of systolic BP was associated with arteriolar narrowing by 2.08 μm (95 % CI: 1.38–2.79, $p<0.0001$), indicative that effects of elevated BP manifest early in life [36].

Regarding TOD data are even more limited. In 1,439 middle-aged African-Americans participants of the Atherosclerosis Risk in Communities Study A/V ratio was associated with measures of left ventricular hypertrophy, which was partly explained by additional CV risk factors and hypertension [13]. In contrast, in an Italian study comprising 386 untreated and treated hypertensive patients, no intergroup differences in A/V ratio was found between presence and absence of acknowledged TOD like left ventricular hypertrophy, carotid intima-media thickness, or microalbuminuria, hence indicating limited value of A/V ratio for identifying patients with high CV risk based on cardiac and extracardiac TOD [38].

There is also an ambiguous picture of arteriolar and venular diameter and different components of CV events. Regarding incident stroke, associations of both arteriolar narrowing and venular widening were reported in some studies, whereas in the Rotterdam Study, only an association of venular widening was found, but not for arteriolar narrowing [30]. Moreover, in the latter Rotterdam Study, venular widening was also associated with intracerebral hemorrhage [31]. These conflicting results are supported based on meta-analyses performed mainly by the META-EYE study group and published in the last years [18, 39].

These conflicting results of the individual components (with respect to arteriolar and venular diameter) have also to be taken into account, when interpreting reported findings about A/V ratio. An altered A/V ratio can be due to single and concurrent changes and their individual amount, and vice versa nonfindings can be seen, for example, by diverging changes.

28.3 Global Geometrical and Branching Parameters (Retinal Vascular Network)

The vasculature is a branching system, and alterations from optimal architecture are proposed to impair function and hence increased vascular damage. Thus, interest has gained on further developments in computer-assisted programs enabling the assessment of several quantitative parameters of retinal vascular network. Using these newly developed retinal vascular parameters, analysis of the Singapore Malay

Eye Study has shown that a combination of smaller retinal vascular fractal dimensions (D_f), proposed to be a global measure of the geometric complexity, and evidence of straighter retinal arterioles indicate poor BP control in treated hypertensive patients [40]. Therefore, retinal alterations can be assumed as pathophysiological markers not only for the severity of hypertension, but also on the effectiveness of drug therapy in hypertension.

Utilizing data from the multiethnic Singapore Prospective Study Program (SP2), the same group has shown that retinal D_f was inversely correlated with BP level in all three ethnic groups. Notably, this was the case in patients with uncontrolled as well as untreated hypertension, but not in patients with controlled hypertension [41].

However, by applying again and again several new parameters, and analyzing these new parameters in the same studies, it is still missing the differentiation which is the most promising and reliable parameter to detect early retinal involvement in the clinical course of hypertension.

28.4 Scanning Laser Doppler Flowmetry (Dynamic)

Funduscopic photographs have the limitation that arteriolar and venular alterations cannot be quantified separately and the vascular wall precisely visualized. Moreover, the term remodeling if assessed in vivo takes two aspects into account, which were interrelated and indistinguishable, namely, morphological changes (i.e., rearrangement of vascular smooth muscle cells) as well as changes of the vascular tone (i.e., endothelial function). To overcome these limitations, one promising approach introduced by our study group about 10 years ago allows the dynamic assessment of both functional and structural parameters by using scanning laser Doppler flowmetry (SLDF) [42]. In brief, SLDF is performed in the juxtapapillary area of the right eye, 2–3 mm temporal superior of the optic nerve at 670 nm (Heidelberg Retina Flowmeter, Heidelberg Engineering, Germany). An arteriole (80–140 μm) of the superficial retinal layer in a retinal sample of $2.56 \times 0.64 \times 0.30$ nm is scanned within 2 s (one systolic and one diastolic phase) and measured every 10 μm of this specific length of the arteriole. The confocal technique of the device ensures that only capillary flow of the superficial layer of 300 μm is measured. The outer arteriole diameter (AD) is measured by reflection images, and the lumen diameter (LD) is measured by perfusion images. Wall-to-lumen ratio (WLR) is calculated using the formula (AD – LD)/LD (Fig. 28.2). Analyses are performed offline with automatic full-field perfusion imaging analysis (AFFPIA) (SLDF Version 4.0 by Welzenbach with improved resolution) [43].

It is noteworthy to mention that assessing both retinal function and structure by SLDF does not require applying any mydriatic drug, which is not only important from the scientific point of view – local application of tropicamide profoundly affects the retinal perfusion [44], but also for patient management perspective (i.e., no constriction of daily routine).

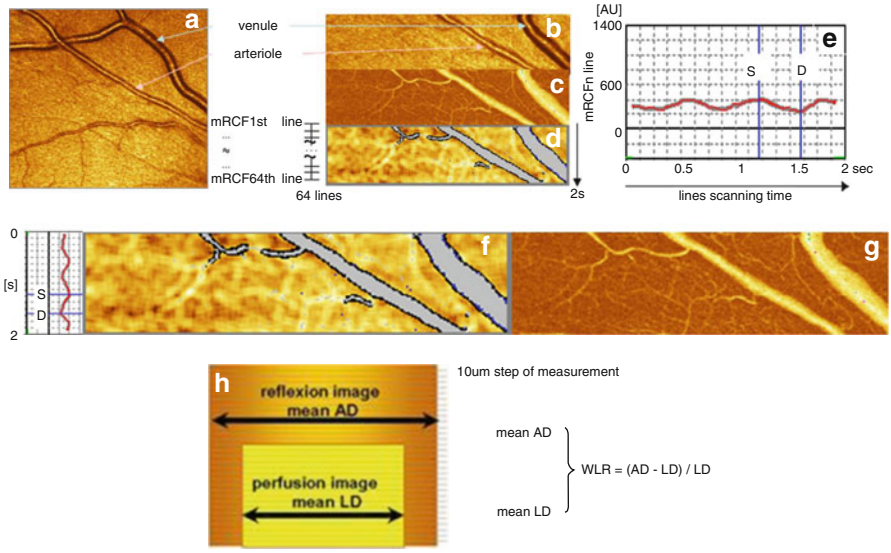

Fig. 28.2 Scanning laser Doppler flowmetry (SLDF). (**a**) Differentiation between retinal arteriole and venule (SLDF live image before measurement). (**b**) Scanned area – reflection image. (**c**) Scanned area – perfusion image. (**d**) Scanned area – corrected and analyzed flow image. (**e**) Pulse curve run as mean retinal capillary flow (*RCF*) and time plot.(**f**) Localization of systolic and diastolic RCF on the image **d**. (**g**) Localization of systolic and diastolic RCF on the image **c**. (**h**) Calculation of wall-to-lumen ratio (*WLR*)

28.5 Retinal Capillary Flow

Due to its common origin from the internal carotid artery, the retinal microcirculation is morphologically and functionally related to the cerebral circulation [45].

Further dynamic information (e.g., basal nitric oxide [NO] activity) of the retinal capillaries can be assessed by measuring changes of retinal capillary flow (RCF) due to nonpharmacological and pharmacological tools. Flicker light increases at least in part via a NO-dependent mechanism and represents a nonpharmacological tool to investigate vasodilatory capacity of retinal capillaries. Notably, flicker light exposure has no effects on systemic BP, thereby minimizing potential systemic hemodynamic influences on RCF. Moreover, basal NO activity is assessed by administration of the NO synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA). Findings in normo- and hypertensive patients are summarized in Table 28.3.

In young hypertensive patients, baseline RCF was similar to normotensive controls. However, assessment of basal NO activity (L-NMMA) revealed an impaired endothelial function in young hypertensive patients, which was improved after treatment with an ARB [42], whereas in elderly hypertensive men treatment with an ARB did not improve RCF at least after short-term treatment of 8 days [46]. Notably, even in

Table 28.3 Studies of our research group, analyzing hypertensive patients and/or patients with cardiovascular event, using scanning laser Doppler flowmetry to assess early vascular changes (in chronological order)

Reference	Patients	Retinal endothelial function	Retinal arteriolar structure
Delles et al. [42]	19 hypertensive men 19 normotensive men	Endothelial function[a] is impaired in essential hypertension and is improved after ARB treatment	
Oehmer et al. [46]	20 (elderly) hypertensive men	Short-term treatment (8 days) with an ARB did not improve retinal endothelial function[a] in elderly hypertensive men	
Harazny et al. [47] (Study 1)	182 normotensive men 117 hypertensive men		WLR is correlated with age in normo- and hypertensive men
Harazny et al. [47] (Study 2)	74 normotensive men 47 hypertensive men 18 men with cerebrovascular event		WLR is higher in subjects with cerebrovascular event than in normo- and hypertensive men Treated patients with poor BP control have higher WLR than patients with good BP control (<140/90 mmHg)
Ritt et al. [48]	21 hypertensive men 19 normotensive men		Systolic and diastolic BP were positively related with WLR, independent from other various cardiovascular risk factors WLR is higher in hypertensive men, but WCSA did not differ between the groups (suggesting eutrophic remodeling)
Baleanu [49]	16 normotensives 83 hypertensives 23 patients with cerebrovascular event		*Arteriovenous ratio were similar between the three groups* Both WLR and WCSA are higher in patients with cerebrovascular event than in normo- and hypertensives *Arteriovenous ratio was not correlated with WLR*

Reference	Patients	Retinal endothelial function	Retinal arteriolar structure
Ritt et al. [50]	89 normotensive men 52 hypertensive men	In normotensive men, vasodilatory capacity[b] was greater in patients above compared to below median RCF In hypertensive men, this was not evident	In hypertensive men, vasodilatory capacity[b] was negatively related to WLR In normotensive men, this was not evident
Raff et al. [51]	40 patients with TRH		WLR, WT, and WCSA were strongly associated with 24-h urinary sodium excretion
Ritt et al. [52]	96 normotensive men 50 hypertensive men	Vasodilatory capacity[b] was higher in normotensive compared to hypertensive patients	
Ott et al. [53]	135 patients with wide BP range		Central PP was an independent determinant of WLR
Harazny et al. [54]	20 hypertensives 19 patients with TRH	Pulsed RCF, but not mean RCF, was higher in patients with TRH compared to hypertensive patients	WT remained unchanged between systole and diastole in patients with TRH, whereas WT changed dynamically in hypertensive patients
Ott et al. [55]	51 patients with TRH	Pulsed RCF, but not mean RCF was reduced by RDN Vasodilatory capacity[b] was increased after RDN	

[a]Change of RCF to L-NMMA infusion

[b]Change in RCF to flicker-light exposure

hypercholesterolemic patients, treatment with an ARB led to a marked BP reduction, which was associated with an improved vasodilatory capacity (flicker light) [56]. In accordance, it was previously shown that vasodilatory capacity (flicker light) was lower in untreated hypertensive patients compared to normotensive controls. Systolic BP was inversely related to the percent increase of RCF due to flicker light exposure, independent of other CV risk factors [52].

Recently, we have shown that also individual pulsatile pattern of RCF (and structural parameters, see below) of retinal arterioles in systole and diastole can be reliably assessed. By doing so, we could show that with advanced stage of hypertensive disease, namely, patients with treatment-resistant hypertension (TRH), pulsed RCF (difference in RCF between systole and diastole) is exaggerated compared to patients with hypertension stages 1–2 [54].

Moreover, further data of our group reveal that BP and hence pulse pressure (PP) changes have an impact on pulsed RCF. In patients with TRH, we observed a decrease of systolic and pulsed RCF 6 and 12 months after renal denervation (RDN), in parallel to decreases of BP and heart rate. The reduction of pulsed RCF after RDN transfers into less shear stress on the vascular wall and, thereby, suggests an improvement of retinal (and potentially cerebral) microcirculation [55].

The importance of these findings is supported by prospective studies showing that, among others, carotid PP and pulsatility index were each associated with an increased risk for silent subcortical infarcts and with lower memory scores [57]. These data suggest that excessive flow pulsatility damages the microcirculation, clinically detectable by impaired cognitive function. Moreover, in a longitudinal study, PP significantly predicted the incidence of stroke (HR 1.33, 95 % CI 1.16–1.51 for each 10 mmHg of PP), which still remained borderline significant ($p = 0.1$) after adjustment for classical CV risk factors [58].

28.6 Structural Parameters of Retinal Arterioles

By using SLDF, also structural parameters of retinal arterioles can be assessed with high reliability [43].

We could show that WLR of retinal arterioles is positively related with systolic and diastolic BP, independent of various other CV risk factors. WLR was higher in never-treated hypertensive patients compared to normotensive controls [48]. Regarding blood pressure control, we found that in patients with poor BP control, WLR is higher than in controlled hypertensive patients [47]. These data are similar to published findings in large-scale population-based studies using retinal funduscopy (see above).

However, in a small cross-sectional study, A/V ratio was not able to discriminate between patients with cerebral event (transient ischemic attack or lacunar cerebral infarct) and normotensive as well as hypertensive patients. In contrast, WLR was significantly higher and could therefore discriminate between patients with cerebrovascular event compared to both normotensive controls and hypertensive patients without cerebrovascular event [49].

In a study comprising patients with wide range of BP values, it was shown that central PP is a strong and independent predictor of WLR (vascular remodeling) beyond "classical" CV risk factors and additional factors that are proposed to have an impact on vascular structure [53]. Such a relationship indicates coupling and intensive cross talk between the micro- and macrovascular changes due to hypertension.

Similar to our RCF analysis, also structural parameters can be assessed according to different heart phases (systole and diastole). In patients with TRH, a stiffer wall of retinal arterioles can be assumed, since wall thickness (WT) remained unchanged between systole and diastole, whereas in patients with hypertension grade 1–2, WT changed dynamically between systole and diastole [54].

Although no data from prospective studies regarding SLDF-assessed WLR and CV events are yet available, indirect, but strong, evidence of the validity for measuring WLR was demonstrated by Rizzoni et al. WLR assessed by SLDF (retinal arterioles in vivo) and media-to-lumen ratio measured with the myograph ex vivo (subcutaneous small arteries taken from a biopsy) showed a close correlation in hypertensive patients, suggesting that SLDF may provide similar information about microcirculation alterations compared to acknowledged prognostic measurement of subcutaneous small arteries, which represent the "gold standard" and prognostically relevant approach to the evaluation of small artery morphology in humans [59]. The absolute values differ due to the different methodologies, e.g., the analysis with myograph takes place ex vivo whereas the SLDF measures the parameters in vivo. The SLDF may underestimate the true internal diameter, since flow diameter does not include any endothelial plasma layer [49].

Nowadays, several other approaches (e.g., adaptive optics and optical coherence tomography) as well as SLDF with another software (e.g., data from Rizzoni et al.) focused on the assessment of WLR of retinal arterioles. It is notable to respect that the methodology of vascular measurements differs between the individual techniques. Therefore, a simple transfer of research findings into clinical practice may not be possible without further validation (see below). An overview of the recent available data is given in Table 28.4.

28.7 Adaptive Optics

Nowadays, available adaptive optics-based fundus cameras are able to assess semi-automatically focal vascular changes (e.g., focal arteriolar narrowing). Moreover, arteriolar morphometry can be applied with a resolution up to near two micrometers, thereby visualizing (among others) vascular wall of retinal arterioles. The feasibility and reproducibility of retinal arterioles imaging was demonstrated in untreated hypertensive patients [62]. Following these pilot investigations, the same authors could show that adaptive optics-based assessment of WLR was positively correlated with mean BP and age which accounted for 43 % of variability of WLR [60]. Although the results on WLR measurements by adaptive optics are close to those reported by SLDF (Table 28.4), it has to be taken into account that no

Table 28.4 Comparison of retinal structural parameters assessed with scanning laser Doppler flowmetry (SLDF), adaptive optics, and optical coherence tomography (OCT)

	SLDF (Ritt et al. [48])		SLDF (Rizzoni et al. [59])		Adaptive optics (Koch et al. [60])		OCT (Muraoka et al. [61])	
	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive	Normotensive	Hypertensive
	($n=29$)	($n=21$)	($n=16$)	($n=24$)	($n=30$)	($n=19$)	($n=83$)	($n=103$)
Age (years)	36.7 ± 5.9		59.3 ± 14		42.3 ± 15		68.5 ± 7.8	
BMI (kg/m^2)	31.5 ± 2.3		25.6 ± 4.4		23.8 ± 4.5			
Systolic BP (mmHg)	129 ± 6.9		125 ± 17		118 ± 13			
Diastolic BP (mmHg)	78 ± 7.6		71 ± 12		74 ± 9.5			
WLR (-)	0.28 ± 0.1		0.26 ± 0.1		0.29 ± 0.1		0.41[b] (mean)	
Outer (vessel) diameter (μm)	109 ± 15		93.6 ± 19		107[a] (mean)		123 ± 9.3	
Inner (lumen) diameter (μm)	85.3 ± 11		74.4 ± 16		83.5 ± 11		87.3 ± 8.3	
Age (years)		39.1 ± 5.4		57.7 ± 15		48 ± 11		69.1 ± 8.1
BMI (kg/m^2)		33.1 ± 4.4		27.4 ± 5.1		26.4 ± 4		
Systolic BP (mmHg)		145 ± 6.8		139 ± 17		154 ± 14		
Diastolic BP (mmHg)		88 ± 8.3		89 ± 10		96 ± 10		
WLR (-)		0.36 ± 0.1		0.37 ± 0.1		0.36 ± 0.1		0.41[b] (mean)
Outer (vessel) diameter (μm)		111 ± 9.6		81.7 ± 20		100[a] (mean)		125 ± 11
Inner (lumen) diameter (μm)		81.8 ± 7.8		59.6 ± 13		74 ± 13		88.5 ± 11

[a]Calculated on the published mean values (lumen diameter + parietal thickness)

[b]Calculated on the published mean values ([outer diameter – inner diameter]/inner diameter)

validation of the method in respect to other available techniques is yet provided. Adaptive optics needs to be directly compared with SLDF measurement or even better, with the media-to-lumen ratio of subcutaneous small resistance arteries assessed by the myographic approach. Adaptive optics examinations may be possible without mydriasis in most but not all cases. Only limited data ($n = 9$) are so far published investigating vascular morphometry before and after locally applied tropicamide. Mean vascular diameter increased only slightly (about 1 %), but data on individual diameters or wall properties are missing [60]. Hence, the effect of locally administered tropicamide cannot be fully excluded.

The major limitation of adaptive optics is that in contrast to SLDF, it cannot measure RCF.

28.8 Optical Coherence Tomography

The optical coherence tomography (OCT) allows the assessment of retinal circulation in an enhanced resolution within an acceptable time period. However, data about the retinal circulation in arterial hypertension are limited. In an analysis of patients (aged over 50 years), it was shown that mean arteriolar outer and inner diameter did not differ between patients with hypertension ($n = 103$, defined by use of antihypertensive medication or physician's diagnosis) and without hypertension ($n = 83$), but mean arterial wall thickness was significantly larger [61]. This is in line with previous findings (unchanged outer and lumen diameter, but higher wall thickness of retinal arterioles) using SLDF in never-treated hypertensive patients compared to controls [48]. However, OCT-measured WLR was higher than previosuly measured with SLDF, perhaps likely attributable to age differences [48], but no direct comparison has so far been made.

Additional features, which can be assessed using OCT, like retinal nerve fiber layer and its importance in hypertension is not determined yet.

28.9 Perspective

Exciting new technologies emerged and offered the opportunities to directly visualize vascular remodeling of small retinal arterioles. The clinical perspective is that the physician may be enabled to diagnose early vascular remodeling to hypertension and tailor the antihypertensive strategy for individual patients. The findings may go beyond the retinal arterioles since the changes in the retinal circulation mirror these in cerebrovascular circulation, one of the major targets of hypertensive disease.

References

1. Schiffrin EL (2004) Remodeling of resistance arteries in essential hypertension and effects of antihypertensive treatment. Am J Hypertens 17:1192–1200

2. Mulvany MJ (2008) Small artery remodelling in hypertension: causes, consequences and therapeutic implications. Med Biol Eng Comput 46:461–467
3. Feihl F, Liaudet L, Levy BI, Waeber B (2008) Hypertension and microvascular remodelling. Cardiovasc Res 78:274–285
4. Keith NM, Wagener HP, Barker NW (1939) Some different types of essential hypertension: their course and prognosis. Am J Med Sci 197:332–343
5. Dimmitt SB, West JN, Eames SM et al (1989) Usefulness of ophthalmoscopy in mild to moderate hypertension. Lancet 1:1103–1106
6. Wong TY, Mitchell P (2004) Hypertensive retinopathy. N Engl J Med 351:2310–2317
7. Downie LE, Hodgson LA, Dsylva C et al (2013) Hypertensive retinopathy: comparing the Keith-Wagener-Barker to a simplified classification. J Hypertens 31:960–965
8. Mancia G, Fagard R, Narkiewicz K et al.; Task Force Members (2013) 2013 ESH/ESC guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31:1281–1357
9. Sharrett AR, Hubbard LD, Cooper LS et al (1999) Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 150:263–270
10. Wong TY, Klein R, Couper DJ et al (2001) Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. Lancet 358:1134–1140
11. Wong TY, Klein R, Sharrett AR et al (2002) Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. JAMA 287:1153–1159
12. Wong TY, Klein R, Sharrett AR et al.; Atherosclerosis Risk in Communities Study (2004) Retinal arteriolar diameter and risk for hypertension. Ann of Intern Med 140:248–255
13. Tikellis G, Arnett DK, Skelton TN et al (2008) Retinal arteriolar narrowing and left ventricular hypertrophy in African Americans. The Atherosclerosis Risk In Communities (ARIC) Study. Am J Hypertens 21:352–359
14. Yatsuya H, Folsom AR, Wong TY, Investigators AS et al (2010) Retinal microvascular abnormalities and risk of lacunar stroke: Atherosclerosis Risk in Communities Study. Stroke 41:1349–1355
15. Wong TY, Klein R, Nieto FJ et al (2003) Retinal microvascular abnormalities and 10-year cardiovascular mortality: a population-based case-control study. Ophthalmology 110:933–940
16. Wong TY, Klein R, Klein BE et al (2003) Retinal vessel diameters and their associations with age and blood pressure. Invest Ophthalmol Vis Sci 44:4644–4650
17. Wong TY, Shankar A, Klein R et al (2004) Prospective cohort study of retinal vessel diameters and risk of hypertension. BMJ 329:79
18. Wang JJ, Liew G, Klein R et al (2007) Retinal vessel diameter and cardiovascular mortality: pooled data analysis from two older populations. Eur Heart J 28:1984–1992
19. Leung H, Wang JJ, Rochtchina E et al (2003) Relationships between age, blood pressure, and retinal vessel diameters in an older population. Invest Ophthalmol Vis Sci 44:2900–2904
20. Leung H, Wang JJ, Rochtchina E et al (2004) Impact of current and past blood pressure on retinal arteriolar diameter in an older population. J Hypertens 22:1543–1549
21. Smith W, Wang JJ, Wong TY et al (2004) Retinal arteriolar narrowing is associated with 5-year incident severe hypertension: the Blue Mountains Eye Study. Hypertension 44:442–447
22. Wang JJ, Liew G, Wong TY et al (2006) Retinal vascular calibre and the risk of coronary heart disease-related death. Heart 92:1583–1587
23. Wong TY, Hubbard LD, Klein R et al (2002) Retinal microvascular abnormalities and blood pressure in older people: the cardiovascular health study. Br J Ophthalmol 86:1007–1013
24. Wong TY, Kamineni A, Klein R et al (2006) Quantitative retinal venular caliber and risk of cardiovascular disease in older persons: the cardiovascular health study. Arch Intern Med 166:2388–2394
25. Wong TY, Islam FM, Klein R et al (2006) Retinal vascular caliber, cardiovascular risk factors, and inflammation: the multi-ethnic study of atherosclerosis (mesa). Invest Ophthalmol Vis Sci 47:2341–2350

26. Kawasaki R, Cheung N, Wang JJ et al (2009) Retinal vessel diameters and risk of hypertension: the multiethnic study of atherosclerosis. J Hypertens 27:2386–2393
27. Yau JW, Xie J, Kawasaki R et al (2011) Retinal arteriolar narrowing and subsequent development of CKD stage 3: the multi-ethnic study of atherosclerosis (MESA). Am J Kidney Dis 58:39–46
28. Ikram MK, de Jong FJ, Vingerling JR et al (2004) Are retinal arteriolar or venular diameters associated with markers for cardiovascular disorders? The Rotterdam Study. Invest Ophthalmol Vis Sci 45:2129–2134
29. Ikram MK, Witteman JC, Vingerling JR et al (2006) Retinal vessel diameters and risk of hypertension: the Rotterdam Study. Hypertension 47:189–194
30. Ikram MK, de Jong FJ, Bos MJ et al (2006) Retinal vessel diameters and risk of stroke: the Rotterdam Study. Neurology 66:1339–1343
31. Wieberdink RG, Ikram MK, Koudstaal PJ et al (2010) Retinal vascular calibers and the risk of intracerebral hemorrhage and cerebral infarction: the Rotterdam Study. Stroke 41:2757–2761
32. Sun C, Liew G, Wang JJ et al (2008) Retinal vascular caliber, blood pressure, and cardiovascular risk factors in an Asian population: the Singapore Malay Eye Study. Invest Ophthalmol Vis Sci 49:1784–1790
33. Sabanayagam C, Shankar A, Koh D et al (2009) Retinal microvascular caliber and chronic kidney disease in an Asian population. Am J Epidemiol 169:625–632
34. Jeganathan VS, Sabanayagam C, Tai ES et al (2009) Effect of blood pressure on the retinal vasculature in a multi-ethnic Asian population. Hypertens Res 32:975–982
35. Sabanayagam C, Tai ES, Shankar A et al (2009) Retinal arteriolar narrowing increases the likelihood of chronic kidney disease in hypertension. J Hypertens 27:2209–2217
36. Mitchell P, Cheung N, de Haseth K et al (2007) Blood pressure and retinal arteriolar narrowing in children. Hypertension 49:1156–1162
37. Ding J, Wai KL, McGeechan K et al (2014) Retinal vascular caliber and the development of hypertension: a meta-analysis of individual participant data. J Hypertens 32:207–215
38. Masaidi M, Cuspidi C, Giudici V et al (2009) Is retinal arteriolar-venular ratio associated with cardiac and extracardiac organ damage in essential hypertension? J Hypertens 27:1277–1283
39. McGeechan K, Liew G, Macaskill P et al (2009) Meta-analysis: retinal vessel caliber and risk for coronary heart disease. Ann Int Med 151:404–413
40. Cheung CY, Tay WT, Mitchell P et al (2011) Quantitative and qualitative retinal microvascular characteristics and blood pressure. J Hypertens 29:1380–1391
41. Sng CC, Wong WL, Cheung CY et al (2013) Retinal vascular fractal and blood pressure in a multiethnic population. J Hypertens 31:2036–2042
42. Delles C, Michelson G, Harazny J et al (2004) Impaired endothelial function of the retinal vasculature in hypertensive patients. Stroke 35:1289–1293
43. Harazny JM, Raff U, Welzenbach J et al (2011) New software analyses increase the reliability of measurements of retinal arterioles morphology by scanning laser Doppler flowmetry in humans. J Hypertens 29:777–782
44. Harazny JM, Schmieder RE, Welzenbach J, Michelson G (2013) Local application of tropicamide 0.5% reduces retinal capillary blood flow. Blood Press 22:371–376
45. Patton N, Aslam T, Macgillivray T et al (2005) Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. J Anat 206:319–348
46. Oehmer S, Harazny J, Delles C et al (2006) Valsartan and retinal endothelial function in elderly hypertensive patients. Blood Press 15:185–191
47. Harazny JM, Ritt M, Baleanu D et al (2007) Increased wall: lumen ratio of retinal arterioles in male patients with a history of a cerebrovascular event. Hypertension 50:623–629
48. Ritt M, Harazny JM, Ott C et al (2008) Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. J Hypertens 26:1427–1434
49. Baleanu D, Ritt M, Harazny J et al (2009) Wall-to-lumen ratio of retinal arterioles and arteriole-to-venule ratio of retinal vessels in patients with cerebrovascular damage. Invest Ophthalmol Vis Sci 50:4351–4359

50. Ritt M, Harazny JM, Ott C et al (2012) Influence of blood flow on arteriolar wall-to-lumen ratio in the human retinal circulation in vivo. Microvasc Res 83:111–117
51. Raff U, Harazny JM, Titze SI et al (2012) Salt intake determines retinal arteriolar structure in treatment resistant hypertension independent of blood pressure. Atherosclerosis 222:235–240
52. Ritt M, Harazny JM, Ott C et al (2012) Impaired increase of retinal capillary blood flow to flicker light exposure in arterial hypertension. Hypertension 60:871–876
53. Ott C, Raff U, Harazny JM et al (2013) Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. Hypertension 61:1340–1345
54. Harazny JM, Ott C, Raff U et al (2014) First experience in analysing pulsatile retinal capillary flow and arteriolar structural parameters measured noninvasively in hypertensive patients. J Hypertens 32:2246–2252
55. Schmieder RE, Ott C, Uder M et al (2014) Retinal microperfusion one year after renal artery denervation in treatment resistant hypertensive patients. J Hypertens 32 (Suppl 1): e69
56. Ott C, Schlaich MP, Harazny J et al (2008) Effects of angiotensin ii type 1-receptor blockade on retinal endothelial function. J Hypertens 26:516–522
57. Wohlfahrt P, Krajcoviechova A, Jozifova M et al (2014) Large artery stiffness and carotid flow pulsatility in stroke survivors. J Hypertens 32:1097–1103; discussion 1103
58. Laurent S, Katsahian S, Fassot C et al (2003) Aortic stiffness is an independent predictor of fatal stroke in essential hypertension. Stroke 34:1203–1206
59. Rizzoni D, Porteri E, Duse S et al (2012) Relationship between media-to-lumen ratio of subcutaneous small arteries and wall-to-lumen ratio of retinal arterioles evaluated noninvasively by scanning laser Doppler flowmetry. J Hypertens 30:1169–1175
60. Koch E, Rosenbaum D, Brolly A et al (2014) Morphometric analysis of small arteries in the human retina using adaptive optics imaging: relationship with blood pressure and focal vascular changes. J Hypertens 32:890–898
61. Muraoka Y, Tsujikawa A, Kumagai K et al (2013) Age- and hypertension-dependent changes in retinal vessel diameter and wall thickness: an optical coherence tomography study. Am J Ophthalmol 156:706–714
62. Rosenbaum D, Koch E, Girerd X et al (2013) Imaging of retinal arteries with adaptative optics, feasibility and reproducibility. Ann Cardiol Angeiol 62:184–188