Literature Reviews

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Precise in vivo adaptive optics imaging of retinal vessels

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Adaptive optics (AO) provides new, unique opportunities for in vivo visualization of retinal vasculature. AO retinal vessel imaging can be utilized as a component of multimodal imaging tools to complement conventional diagnostic imaging modalities. Non-invasive and highly promising AO imaging of fundus structures allows the qualitative and quantitative assessment of early signs of retinal vascular remodeling associated with age, arterial hypertension, diabetes mellitus and other disorders.

Keywords:
adaptive optics, retinal vessels, arterial hypertension, diabetic retinopathy

The use of adaptive optics (AO) in optical imaging systems (such as telescope, microscope and retinal camera) enables compensating the aberrations which appear during the propagation of light in inhomogeneous media, leading to obtaining images of significantly improved quality and resolution.[1] Thus, such a technique has been widely employed in ground-based telescopes [2, 3] to measure and correct atmospheric aberrations, allowing the formation of high-quality images of the astronomical objects (e.g., extrasolar planets) that are difficult to discriminate. In neurobiological applications, AO imaging enhances opportunities for in vivo assessment of the structure and function of the neurons located at a certain depth in the brain of experimental animals through the correction of wavefront aberrations.[4, 5]

In addition, AO imaging has been applied in ophthalmology for high-accuracy visualization of retinal cells and vessels.[6] Photoreceptor cones were among the first retinal cells to be visualized and quantitatively assessed in vivo using instrumentation equipped with AO.[7] Since then, novel engineering solutions in AO fundus imaging systems have led to fast evolution of the method and improved quality of images of different retinal structures. It has been reported more recently that not only images of individual photoreceptor cones and rods, but also images of individual ganglion cells and pigment epithelial cells of the retina and other structures can be obtained.[8-12]

The operating principle of the above high-resolution retinal imaging devices is based on the AO correction of monochromatic high-order aberrations caused by the crystalline lens and the retina.[6, 7] A beam of incoherent light-emitting diode (LED) or laser-generated light is delivered into the eye transpupillary or transsclerally,[12] and a small amount is reflected from the retina back out of the eye and into the optical system. The aberrations in the reflected signal introduced by the optical structures of the eye are detected and measured by a wavefront sensor, processed by a control unit, and corrected for by an adaptive deformable mirror.[13, 14] Figure 1 shows a schematic of an AO retinal imaging system.

In recent years AO technology has been successfully integrated with the three primary ophthalmic imaging devices (conventional fundus camera, scanning laser ophthalmoscope, and optical coherence tomograph.[6, 14-19] Using a fundus camera equipped with AO has become one of the first examples of successful high-precision two-dimensional AO retinal imaging applications. With this approach, images of photoreceptors and retinal vessels can be acquired in a relatively short time, minimizing the effect of eye movement. However, this approach limits the axial resolution of images.[14] AO scanning laser ophthalmoscopy enables two-dimensional imaging with better contrast and axial resolution than the AO fundus camera.[17] AO ocular coherence tomography (OCT) enables three-dimensional slice-by-slice imaging of the retina with ultra-high axial and transverse resolution required for the visualization of individual cells.[19]

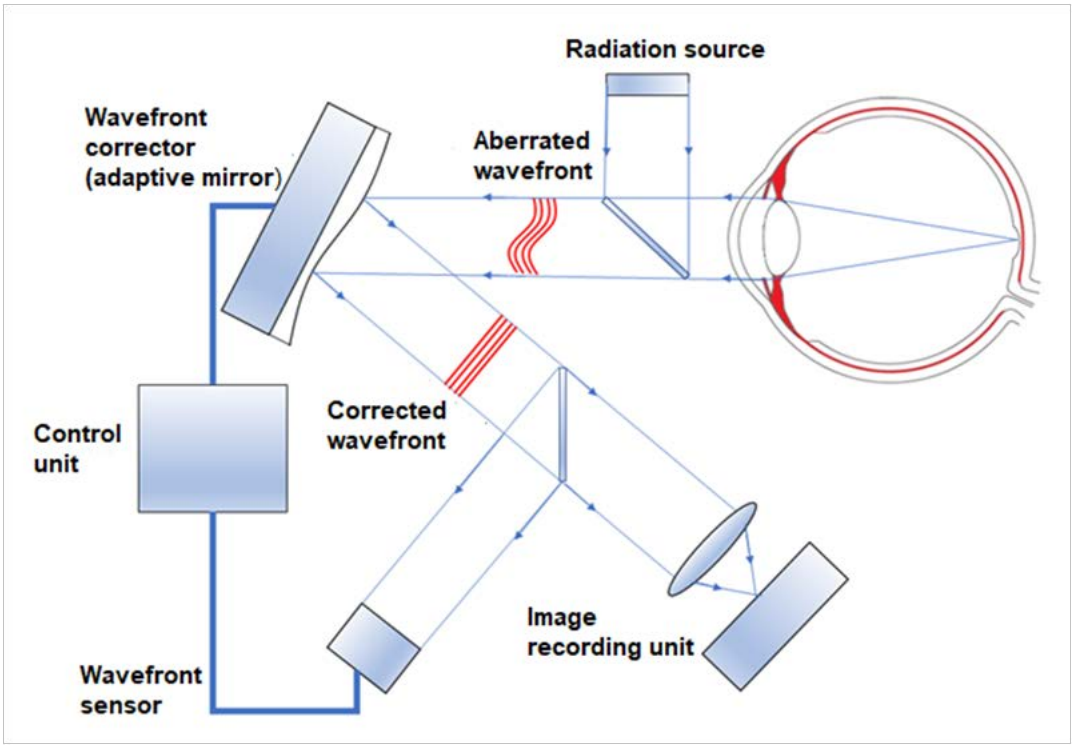

Fig. 1. Schematic of an AO retinal imaging system

Retinal vessel imaging

In vivo AO imaging of retinal vessels is promising for identification of new biomarkers for vascular disorders, both ocular and systemic.[20, 21] The method allows qualitative and quantitative microvascular morphometry of small human retinal vessels at a near-histological scale.[22] Figure 2 shows an image of retinal arteriole obtained with the Filatov institute AO fundus camera (RTX-1, Imagine Eyes, Orsay France).

Imaging modalities enhanced with AO allow for high-resolution in vivo visualization of 10-100 μm diameter vessels of the retinal microcirculation.[20, 23] By applying AO to conventional imaging modalities, the mictostructures of the retinal arteriole wall can be observed with high spatial resolution, and local changes in outer diameter (OD) and inner diameter (ID) of the retinal arteriole, as well as changes in the perivascular tissues can be determined.[15] Typically, the mural cells around venules appeared as flat and elongated in shape when compared with the mural cells in arterioles with comparable lumen diameter and were more difficult to image, and venular wall components were not readily

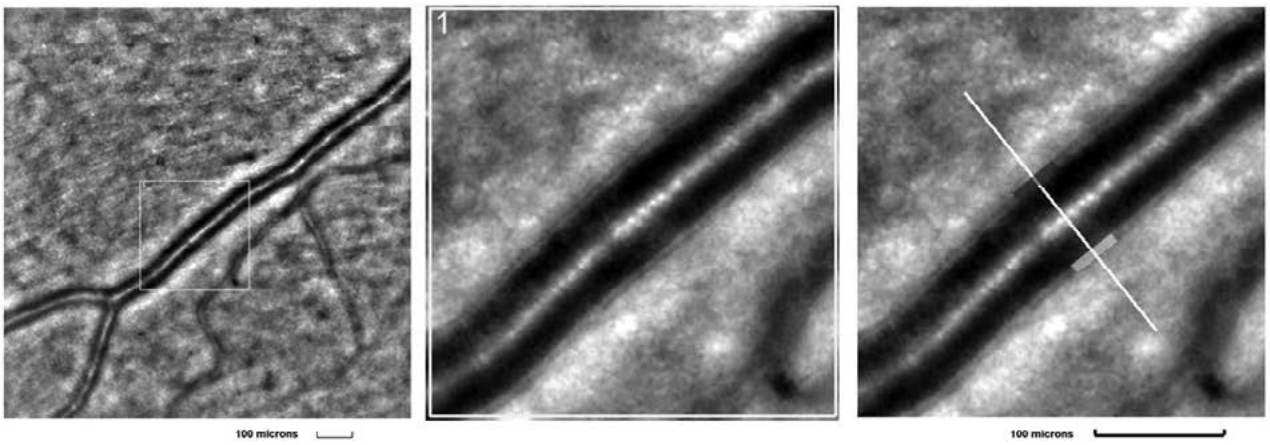

Fig. 2. Images of a normal retinal arteriole obtained with the Filatov institute AO fundus camera (RTX-1, Imagine Eyes, Orsay France). Vascular wall thickness: 7.9 μm and 7.9 μm; wall-to-lumen ratio: 0.25

identified.[20] Vascular wall components of parafoveal capillaries are even more difficult to image due to small size of these vessels.

Bakker and colleagues [15] found that ID (also reported as lumen diameter or lumen width), OD, parietal thickness (PT; also reported as vessel wall thickness), wall cross sectional area (WCSA) and wall-to-lumen ratio (WLR) are the five most commonly used retinal vascular biomarkers imaged by AO flood illumination ophthalmoscopy (FIO) and AO scanning laser ophthalmoscopy (SLO).

Retinal arteriole WLR was the most commonly analyzed parameter in the papers reviewed by us. On the basis of invasive micromyographic evaluation of subcutaneous small arteries (100 to 280 μm average diameter in relaxed conditions), Rizzoni and colleagues [24] found that the tunica media–to–internal lumen ratio (M/L) was significantly associated with the occurrence of cardiovascular events, indicating the prognostic significance of this factor.

In a study by Hillard and colleagues [23], the OD of retinal arterioles from less than 10 to over 150 μm were measured in healthy normotensive individuals using a multiply scattered light AOSLO. The authors found that WLR varied with vessel diameter, and was the largest (0.41 ± 0.23) in the smallest arterioles of 10 to 50 μm.

Others used the technique of AO retinal imaging to measure the WLR of retinal arterioles and found that age was significantly associated with increased WLR. WLR was 57% in the group of subjects older than 60 years and 30% higher in the group of subjects of 40 to 59 years than in the group of subjects of 20 to 39 years.[25-27] Therefore, it can be said that age-related remodeling of the retinal arterioles is caused by an increase in their parietal thickness, leading to an increase in WLR. [25, 27]

Table 1 shows ID, OD and WLR values for retinal vessels measured by different techniques in healthy subjects as reported by different studies.

In the literature that we reviewed, retinal vessels with an OD exceeding 50 μm had mean WLR values ranging from 0.22 to 0.39 in healthy subjects, with the mean plus or minus standard deviation (SD) WLR values found to be the highest (0.39 ± 0.09) for the group of healthy individuals with a mean age plus or minus SD of 60 ± 8 years.[35]

AO imaging also allows identifying and quantitatively assessing some types of retinal mural cells. Thus, cells with a prominent cell body (most likely pericytes) were found on the outer wall of small arterioles and venules. It was noted that there was a morphological difference between venule pericytes and arteriole pericytes. It is difficult to detect and quantitatively assess pericytes and

Table 1. Outer and inner diameters and wall-to-lumen ratio for retinal vessels in normal subjects

Publication authors	Year	Method	Subject age, years	Outer vessel diameter, μm	Inner vessel diameter, μm	Wall-to-lumen ratio
Baleanu D., et al.[28]	2009	SLDF	52.2 ± 8.3	110.6 ± 13.4	85 ± 10.9	0.30 ± 0.1
Rizzoni D., et al.[29]	2012	SLDF	59.3 ± 13.6	93.6 ± 18.9	74.4 ± 15.6	0.264 ± 0.11
Koch E., et al.[26]	2014	AO-FIO	42.3 ± 15		83.5 ± 11.2	0.285 ± 0.05
Salvetti M., et al.[30]	2014	SDLF	55 ± 4	80 – 140		0.23 ± 0.13
Meixner E., et al.[25]	2015	AO-FIO	36.9 ± 17.9			0.26 ± 0.04
Arichika S., et al.[27]	2015	AOSLO	60.6 ± 6.3	128.2 ± 13.1	100.4 ± 11.5	0.28 ± 0.04
Hillard J.G., et al.[23]	2016	AOSLO	37.5 ± 16	10 – 50 > 50		0.41 ± 0.23** 0.234 ± 0.08**
Rosenbaum D., et al.[22]	2016	AO-FIO	52.5 ± 13.3		79.0 ± 11.4	0.285 ± 0.055
Zaleska-Żmijewska A., et al.[31]	2017	AO-FIO	42.4 ± 14.3		105.6 ± 14.6	0.22 ± 0.04
Arichika S., et al.[32]	2017	AOSLO	54.5 ± 11.0	125.2 ± 12.1	101.8 ± 11.2	
Zaleska-Żmijewska A., et al.[33]	2019	AO-FIO	46.0 ± 10.0	113.4 ± 32.2	96.2 ± 11.8	0.254 ± 0.033
Cristescu I.E., et al.[34]	2019	AO-FIO	39.6 ± 5.64	94.87 ± 18.7	76.27 ± 15.4	0.24 ± 0.035
Streese L., et al.[35]	2020	AO-FIO	24 ± 2 60 ± 8		226 ± 53 206 ± 49	0.31 ± 0.08* 0.39 ± 0.09*
Ueno Y., et al.[36]	2021	AO-FIO	67.2 ± 10.1	120.1 ± 14.7	94.6 ± 11.95	0.27 ± 0.03
Sadowski J., et al.[37]	2022	AO-FIO	69 (66–75)	> 50		0.27(0.26-0.31)^
Baltă F., et al.[38]	2022	AO-FIO	44.8 ± 12.9	93.7 ± 14.06	75.7 ± 11.64	0.24 ± 0.046

Note: SLDF, scanning laser Doppler flowmetry; AO-FIO, AO flood illumination ophthalmoscopy; AOSLO, AO scanning laser ophthalmoscopy; ^, median [interquartile range]; *, p = 0.012; **, p < 0.0001.

Outer diameter, inner diameter (or lumen) and wall-to-lumen ratio values are presented as mean plus or minus standard deviation.

endothelial cells in vessels with a diameter less than 10 μm because in AO ophthalmoscopy the detection is limited by the resolution of the system.[20] Therefore, despite advances in in vivo imaging of vascular mural cells of retinal arterioles and venules, there is a need for further research and new technical solutions in this field.

The use of AO in a confocal scanning laser ophthalmoscope (AOSLO) allows for long-term imaging of parafoveal capillary leukocyte movement and measurement of leukocyte velocity without contrast dyes. [39] The mean plus or minus SD parafoveal capillary leukocyte velocity for healthy subjects with clear ocular media was 1.30 ± 0.40 mm/s.[40]

AO imaging of retinal vessels in some disorders

Microcirculation vessels undergo structural and functional changes in primary arterial hypertension (AH). [22, 41, 42] Remodeling of arterioles with an increase in WLR values is a feature of microvascular lesions in target organs. [22, 43] Koch and colleagues [26] used a commercially available flood illuminated AO retinal camera to show increased WLR in AH, with the results suggesting that smaller vessels are better indicators of hypertensive changes in the human eye. Others also reported that WLR values were higher in hypertensive compared to normotensive subjects.[23, 25, 30]. In the literature that we reviewed, AO imaging demonstrated that mean WLR values in retinal vessels with a diameter exceeding 50 μm were higher for patients with AH compared to healthy controls (0.3 to 0.36 versus 0.23 to 0.285, respectively). Park and Schiffrin [44] hypothesized that small artery structural remodeling may precede most clinically relevant manifestations of target organ damage in mild essential hypertension. Therefore, WLR values allow the assessment of arteriole remodeling at an early phase of AH-associated vessel alteration.

Age and AH are significantly associated with an increased WLR of retinal arterioles.[25, 27]. Blood pressure and age independently result in an increase in arterial wall thickness and, consequently, an increase in WLR. In hypertensive individuals, a short-term drug-induced blood pressure drop was followed by a WLR decrease because of lumen dilatation without wall thickness changes.[22] Hypertensive patients with poor blood pressure control showed larger WLR values than subjects with good blood pressure control.[45, 46] Therefore, adequate blood pressure control enables the protection from AH-induced arteriole damage.

Table 2 shows retinal vessels ID, OD and WLR values measured by different techniques in patients with AH as reported by different studies.

The findings of a study by Sadowski and colleagues [37] suggested gradual and simultaneous progression of vascular remodeling in both retinal arterioles and carotid arteries in patients with heart failure with preserved ejection fraction.

AO imaging systems are helpful in detecting early signs of retinal arteriole remodeling in patients with diabetes mellitus, including those with no signs of diabetic retinopathy (DR). Thus, diabetic patients without DR showed larger retinal arterial wall thickness and WLR values compared to healthy individuals.[32, 34, 38] Therefore, retinal arteriole wall thickness and WLR can be considered as early biomarkers of microangiopathy in diabetic patients.

Table 2. Outer and inner diameters and wall-to-lumen ratio for retinal vessels in patients with arterial hypertension

Publication authors	Year	Method	Subject age, years	Outer vessel diameter, μm	Inner vessel diameter, μm	Wall-to-lumen ratio
Baleanu D., et al.[28]	2009	SLDF	53.7 ± 5.5 57.5 ± 9.4	107 ± 10.9 110.7 ± 13.5	80 ± 9.2 76.5 ± 6.45	0.34 ± 0.1 0.44 ± 0.1 ^
Rizzoni D., et al.[29]	2012	SLDF	57.7 ± 4.6	81.7 ± 19.5	59.6 ± 13.4	0.37 ± 0.09
Koch E., et al.[26]	2014	AO-FIO	48.0 ± 11		74 ± 12.6	0.36 ± 0.08
Salvetti M., et al.[30]	2014	SDLF	53 ± 8 55 ± 7	80 – 140 80 – 140		0.28 ± 0.18 × 0.29 ± 0.18 ××
Arichika S., et al.[27]	2015	AOSLO	60.9 ± 4.7	121.7 ± 19.2	92.9 ± 15.9	0.315 ± 0.066
Hillard J.G., et al.[23]	2016	AOSLO	52.9 ± 13.7	10 – 50 > 50		0.70 ± 0.38 0.303 ± 0.08
Rosenbaum D., et al.[22]	2016	AO-FIO	56.1 ± 12.8		75.4 ± 11.9 73.3 ± 8.8	0.304 ± 0.054 * 0.342 ± 0.072 **

Note: SLDF, scanning laser Doppler flowmetry; AO-FIO, AO flood illumination ophthalmoscopy; AOSLO, AO scanning laser ophthalmoscopy; ^, patients with arterial hypertension-induced cerebrovascular damage; ×, untreated hypertensive patients; ××, treated patients with essential hypertension; *, hypertensive individuals with a drug-induced blood pressure drop; **, hypertensive individuals without a drug-induced blood pressure drop. Outer diameter, inner diameter (or lumen) and wall-to-lumen ratio values are presented as mean plus or minus standard deviation.

Detailed images of remodeled vessels and individual microaneurysms in the retina of patients with DR can be obtained by AOSLO without the need for any exogenous contrast agent.[47, 48]

As diabetic retinopathy progresses, retinal vessel lumen decreases, and the parietal thickness and the wall-to-lumen ratio increase. In the literature that we reviewed, mean WLR values of retinal vessels as assessed by AO imaging were larger in diabetic patients than in controls, ranging from 0.29 to 0.5 in diabetic patients and from 0.22 to 0.27 in healthy individuals. The mean WLR measured by AO camera was significantly higher in the proliferative DR groups than in non-proliferative DR (NPDR) groups and controls.[36, 38]

Table 3 shows retinal vessels ID, OD and WLR values in diabetic patients as reported by different studies.

Lombardo and colleagues [49] used AO imaging to demonstrate that the parafoveal capillaries were narrower in patients with type 1 diabetes and NPDR than in healthy subjects. Thus, the average capillary lumen caliber was significantly narrower in eyes with NPDR (6.27 ± 1.63 μm) than in the control eyes (7.31 ± 1.59 μm, p = 0.002).

AO retinal imaging systems may be helpful for the assessment of not only retinal arterial remodeling, but also retinal venous remodeling.[50-52]

Therefore, AO retinal imaging systems (1) allow for non-invasive and high-accuracy assessment of the wall structure and lumen of vessels, perivascular tissues and individual microaneurysms, and detection of early signs of retinal vascular remodeling, and (2) may be a helpful component of multimodal retinal imaging or provide complementary data to conventional techniques (fluorescein angiography (FA) and PCT angiography (OCT-A)) in patients with vascular disorder.

Multimodal fundus imaging comprises the use of more than one technological system to acquire fundus images, concurrently or at a short period of time, that complement one another for the purpose of diagnosis, prognostication, management, and monitoring of the retinal disease. Each modality has unique advantages and limitations. When analyzed together, different imaging modalities can increase diagnostic sensitivity and specificity.[53, 54]

The use of AO can result in an improvement in OCTA and FA image quality. Thus, OCTA uses intrinsic motion contrast provided by the flowing blood cells to allow visualization of the retinal vascular network, but visualization of the capillary caliber is limited by the low lateral resolution. Camino and colleagues [55] demonstrated the benefits of a sensorless AO-OCTA instrument in producing OCTA images with improved contrast, and visualization of capillary caliber, as well as reduced prevalence of projection artifacts. FA has been a golden standard for assessing retinal vascular circulation and vascular wall permeability via visualization of the intravenously administered dye. However, the quality of images obtained with FA is low for studies of vascular wall structure. FA, coupled with confocal AOSLO, has enhanced the success of imaging the retinal microvasculature of the macula and peripapillary retina. This has been used to show perfusion and non-perfusion of the retinal microvasculature and to ptovide additional structural information such as fine structural components of vascular walls.[56]

Table 3. Outer and inner diameters and wall-to-lumen ratio for retinal vessels in patients with diabetes mellitus

Publication authors	Year	Method	Subject age, years	Outer vessel diameter, μm	Inner vessel diameter, μm	Wall-to-lumen ratio
Zaleska-Żmijewska A., et al.[31]	2017	AO-FIO	52.6 ± 10.0		94.3 ± 10.9	0.29 ± 0.05 ^
Arichika S., et al.[32]	2017	AOSLO	53.1 ± 9.6	128.0 ± 15.5	101.8 ± 14.6 *	
Zaleska-Żmijewska A., et al.[33]	2019	AO-FIO	49.0 ± 8.0	126.9 ± 12.9	94.2 ± 12.2	0.339 ± 0.06 **
Cristescu I.E., et al.[34]	2019	AO-FIO	38.06 ± 6.87 54.42 ± 9.47	83.12 ± 22.5 92.49 ± 18.18	71.31 ± 22.4 71.82 ± 14.5	0.31 ± 0.75 * × 0.29 ± 0.58 * ××
Ueno Y., et al.[36]	2021	AO-FIO	62.7 ± 12.9 63.4 ± 12.7 55.1 ± 12.6 59.7 ± 11.8	122.57 ± 18.6 122.93 ± 13.2 119.06 ± 11.2 122.69 ± 11.1	93.21 ± 15.4 91.60 ± 11.4 89.35 ± 9.64 82.31 ± 11.7	0.31 ± 0.04 * 0.34 ± 0.07 ** 0.33 ± 0.03 ** 0.50 ± 0.11 ***
Baltă F., et al.[38]	2022	AO-FIO	53.68 ± 20.16 56.24 ± 10.84 55.71 ± 13.06	94.3 ± 22.21 111.78 ± 30.2 97.16 ± 26.66	73.12 ± 19.52 88.73 ± 30.45 73.85 ± 24.95	0.3 ± 0.073 * 0.29 ± 0.11 ** 0.34 ± 0.1 ***

Note: SLDF, scanning laser Doppler flowmetry; AO-FIO, AO flood illumination ophthalmoscopy; AOSLO, AO scanning laser ophthalmoscopy; ^, patients with prediabetes as per the American Diabetes Association; *, patients with diabetes mellitus (×, type 1 diabetes mellitus, ××, type 2 diabetes mellitus) without DR; **, patients with non-proliferative diabetic retinopathy; ***, patients with proliferative diabetic retinopathy. Outer diameter, inner diameter (or lumen) and wall-to-lumen ratio values are presented as mean plus or minus standard deviation.

AO fundus imaging still has some limitations. High-quality AO images of fundal components may be difficult to obtain in patients with dry eye, cataract, corneal and vitreous opacities, and nystagmus. Although there is a variety of results of studies focused on the assessment of vascular biomarkers, AO fundus imaging protocols have not been developed, and standards for the assessment of vascular biomarkers have not been yet approved.[15, 53]

Conclusion

AO retinal vessel imaging can be utilized as a component of multimodal imaging to complement FA and OCTA for the purpose of diagnosis, prognostication, management, and monitoring of various retinal disorders. Non-invasive and highly promising AO imaging of fundus structures allows the qualitative and quantitative assessment of early signs of retinal vascular remodeling associated with age, arterial hypertension, diabetes mellitus and other disorders. Standard protocols should be developed and approved for AO fundus imaging and assessment of vascular biomarkers in different retinal disorders.

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Abbreviations: *AO, adaptive optics; AH, arterial hypertension; DM, diabetes mellitus; DR, diabetic retinopathy; FA, fluorescein angiography; OCTA, ocular coherence tomography angiography*