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The New Era of Retinal Imaging in Hypertensive Patients

Wilson Tan†, Xinwen Yao, PhD*‡§, Thu-Thao Le, PhD¶||, Bingyao Tan, PhD*‡§*
Leopold Schmetterer, PhD‡§||**††‡‡, Jacqueline Chua, BOptom PhD*||*

Abstract: Structural and functional alterations in the microcirculation by systemic hypertension can cause significant organ damage at the eye, heart, brain, and kidneys. As the retina is the only tissue in the body that allows direct imaging of small vessels, the relationship of hypertensive retinopathy signs with development of disease states in other organs have been extensively studied; large-scale epidemiological studies using fundus photography and advanced semi-automated analysis software have reported the association of retinopathy signs with hypertensive end-organ damage includes the following: stroke, dementia, and coronary heart disease. Although yielding much useful information, the vessels assessed from fundus photographs remain limited to the larger retinal arterioles and venules, and abnormalities observed may not be that of the earliest changes. Newer imaging modalities such as optical coherence tomography angiography and adaptive optics technology, which allow a greater precision in the structural quantification of retinal vessels, including capillaries, may facilitate the assessment and management of these patients. The advent of deep learning technology has also augmented the utility of fundus photographs to help create diagnostic and risk stratification systems. Particularly, deep learning systems have been shown in several large studies to be able to predict multiple cardiovascular risk factors, major adverse cardiovascular events within 5 years, and presence of coronary artery calcium, from fundus photographs alone. In the future, combining deep learning systems with the imaging precision offered by optical coherence tomography angiography and adaptive optics could pave way for systems that are able to predict adverse clinical outcomes even more accurately.

Key Words: adaptive optics, deep learning, hypertension, OCTA, optical coherence tomography angiography

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Systemic hypertension remains the leading contributor to the global burden of disease and global all-cause mortality,[1] and microcirculation plays an important role in the pathophysiology of hypertension.[2] In the early phase of hypertension, arteries, and arterioles frequently constrict because of a variety of nervous or endocrine, and autocrine mechanisms.[2,3] In the chronic phase, these functional changes of vascular constriction become more structural, as distinguished by inward hypertrophy of arteries and arterioles accompanied by the ongoing rarefaction of arterioles and capillar-ies.[2,3] These structural alterations not only result in the chronic elevation of high blood pressure, but also lead to impaired tissue perfusion to various end organs, such as the heart, brain, and kidneys, substantially increasing the risk of morbidity and mortality.

The management of hypertension involves the reduction of blood pressure levels but can be enhanced by assessing and prognosticating end-organ damage. Current assessment of endorgan damage, however, relies on biochemical parameters or ultrasound / magnetic resonance / computed tomography imaging. Direct visualization of the microcirculation is largely lacking, because of limited resolution of the imaging techniques. In this review, we will focus on the clinical applicability of advanced ocular imaging techniques, such as optical coherence tomography angiography (OCTA) and adaptive optics (AO) technology relevant to the management of systemic hypertension.

FUNDUS PHOTOGRAPHY

In the retina, where blood vessels are directly visible, the changes related to hypertension can be viewed by clinicians during ophthalmological examination and assessed as hypertensive retinopathy. The current systems of grading hypertensive retinopathy, the Keith-Wagner-Barker or Wong-Mitchell classification systems (Table 1), are based on the classification of hypertensive retinopathy into different severities, depending on the detection of retinal signs, such as arteriolar narrowing, arteriovenous nicking, and dot-blot hemorrhages[4] (Fig. 1). Except in its severe stage, hypertensive retinopathy alone is not expected to cause vision loss. Therefore, the significance of hypertensive retinopathy has progressively shifted

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From the *Singapore Eye Research Institute, Singapore National Eye Centre, Singapore; †Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore; ‡School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore; §SERI-NTU Advanced Ocular Engineering (STANCE), Singapore, Singapore; ¶National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore; ||Ophthalmology and Visual Sciences Academic Clinical Program, Duke-National University of Singapore Medical School, Singapore; **Department of Clinical Pharmacology, Medical University of Vienna, Austria; ††Center for Medical Physics and Biomedical Engineering, Medical University of Vienna, Austria; and ‡‡Institute of Molecular and Clinical Ophthalmology, Basel, Switzerland
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Address correspondence and reprint requests to: Jacqueline Chua, Singapore Eye Research Institute, 20 College Road, The Academia, Level 6, Discovery Tower, Singapore 169856. E-mail: jacqueline.chua.y.m@seri.com.sg
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Table 1. Current Classification Systems for Hypertensive Retinopathy

Keith-Wagner-Barker Classification System[93] and Associated Clinical Features		Wong-Mitchell Classification System[94] Clinical Features and Associated Classification System		Systemic Associations Proposed by Wong and Mitchell[94] for the Wong-Mitchell
Grade 1	Generalized arteriolar narrowing	Mild	Generalized/focal arteriolar narrowing, arteriovenous nicking, opacity of arteriolar wall ("copper wiring"), or combination of these signs	Modest association with risk of stroke. However, association has only been specifically observed for generalized arteriolar narrowing and arteriovenous nicking.[95]ĆModest association with coronary heart disease. However, association has only been specifically observed for focal/ generalized arteriolar narrowing, and arteriovenous nicking.[96,97] Modest association with death. However, association has only been specifically observed for focal/generalized arteriolar narrowing, and arteriovenous nicking, in middle-aged persons.[98]
Grade 2	Focal narrowing and arteriovenous nicking			
Grade 3	Grade 2 plus exudates, hemorrhages, and cotton wool spots	Moderate	Soft/hard exudates, hemorrhages (flame, dot, blot), microaneurysms, or combination of these signs	Strong association with risk of stroke. However, association has only been specifically observed for microaneurysms, soft exudates, blot hemorrhages and flame-shaped hemorrhages.[95]ĆStrong association with cognitive decline. However, association has only been specifically observed for microaneurysms, retinal hemorrhage, and soft exudates.[99]ĆStrong association with death from cardiovascular causes. However, association has not been demonstrated with any specific parameter.[98]
Grade 4	Grade 3 plus optic disc swelling	Malignant	Moderate grade plus optic disc swelling	Strong association with death. However, no studies support this conclusion.

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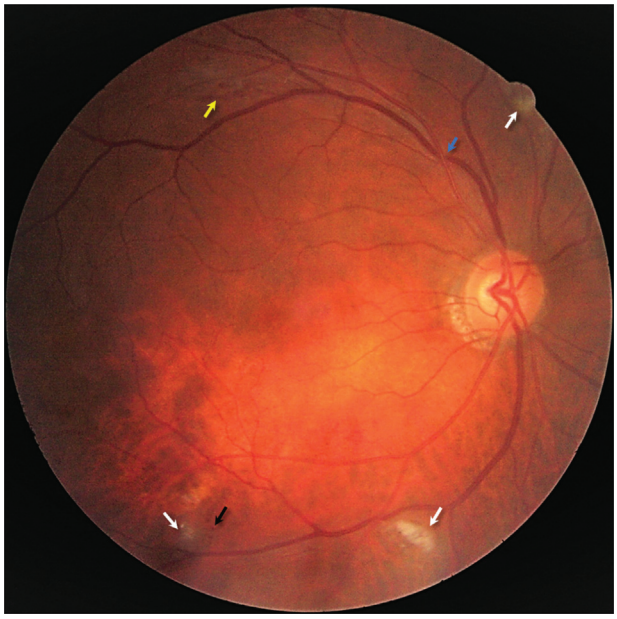

Figure 1. Arteriovenous nicking (blue arrow), cotton wool spots (white arrows), flame-shaped (black arrow), and dot-blot hemorrhages (yellow arrow), and microaneurysms (black arrows) in an eye with moderate hypertensive retinopathy.

to a marker and prognostic factor for end-organ damage, namely in the heart, brain, and kidneys.[5]

Potential Biomarkers Obtained From Fundus Photographs

Over the last 3 decades, epidemiological studies from multiple countries such as the US,[6,7] the UK,[8] Denmark,[9] Holland,[10] Norway,[11] Australia,[7,12] Japan,[13] Singapore,[14] and China[15] have used standardized fundus photographs and semi-automated image processing technologies to quantitatively measure retinal vascular geometric parameters, including vessel diameter, focal narrowing, fractal branching architecture, and tortuosity.[16] The earlier studies were performed predominantly in patients with hypertension and diabetes because microcirculation had increasingly been recognized for its role in these diseases at that time. These preliminary studies essentially corroborated previous microvascular observations in animal models of hypertension that showed arteriolar narrowing resulting from intimal thickening and medial hyperplasia, hyalinization, and sclerosis of arteriolar walls.[17]

Furthermore, the narrowing of arterioles may be a hallmark of the early stages of hypertension. Indeed, a meta-analysis of long-term epidemiological follow-up studies observed that "normotensive" persons with generalized retinal arteriolar narrowing were more likely to develop hypertension.[18] This confirmed the idea that retinal imaging could provide a new source of information. Because the retinal microvascular changes can already be visualized in preclinical stages of hypertension, retinal imaging could have predictive power for the development and related risk of end-organ damage.

Apart from the development of hypertension, several studies[6,12] have observed that retinopathy signs such as generalized arteriolar narrowing and arteriovenous nicking have been associated with both current and past blood pressure levels, suggesting that these signs could be particularly helpful in assessing persistent microvascular changes from hypertension. The quantitative assessment of retinal microvascular geometry characteristics from these imaging techniques shows high reproducibility and can be used repeatedly in the same person for follow-up studies.[19]

Use of Fundus Photographs for End-Organ Disease Prognostication

Studies have also reported relationships of retinal microvascular changes with end-organ damage (Table 1). In terms of the heart, retinal arteriolar narrowing and venular widening were found to have links with coronary heart disease in females,[20,21] and long-term mortality risk and ischemic stroke in both males and females.[21] A review of these studies can be found in a 2019 meta-analysis paper.[22] They observed that retinal arteriolar, but not venular caliber, was consistently correlated with large arterial function and large arterial structure, particularly in patients with cardiometabolic disease. One notable conclusion of this meta-analysis was that preclinical changes in the microcirculation and large arteries have some shared but mainly unique pathways associated with cardiovascular disease. This suggests that retinal microvascular changes have predictive power for the development of cardiovascular risk.

A recent review conducted on the associations between retinal microvascular signs and heart diseases[23] suggested that the retinal microvasculature can provide essential data about concurrent cardiac disease status and predict future risk of cardiac-related events. An interesting finding of this review is that vessel diameters, particularly narrower arterioles in combination with wider venules, correlate with the incidence of acute coronary syndrome, especially in women, and can predict its development. This gender discrepancy supports the hypothesis that microvascular dysfunction plays a greater role in the pathogenesis of coronary heart disease in women than in men. Another important finding from this review is that apart from vessel diameters, other structural characteristics of the retinal vessels, such as branching angles and tortuosity, are associated with heart disease and mortality.

Apart from cardiovascular risks, retinal imaging can also provide information on the early signs of brain-related risks, such as the development of (vascular) dementia.[24] Several studies have demonstrated that the presence of arteriolar narrowing and venular widening is associated with the incidence of stroke,[25,26] and the incidence of lacunar strokes.[27,28] Retinal hemorrhages were also associated with cerebral hemorrhages.[29,30] Furthermore, venular widening has also been observed to have links with incident dementia,[31] prevailing dementia,[32,33] and prevailing Alzheimer disease[34] independent of age, blood pressure, and traditional risk factors. Indeed, a recent review by Rim and coworkers[35] found that both qualitatively and quantitatively assessed parameters on fundus photography were consistently associated with clinical cerebrovascular disease, including clinical stroke, cerebral hemorrhage, and stroke mortality. These parameters were also found to be associated with subclinical cerebrovascular disease, including subclinical cerebral large artery infarction, lacunar infarction, and white matter lesions identified on magnetic resonance imaging. These patterns of association between retinal changes with brain-related risks and diseases are not unexpected because the retinal vessels share similarities with the brain in terms of vascular development and likelihood abnormalities.[24]

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There were fewer studies investigating the association between retinal microvascular signs and kidney diseases in hypertensive patients. However, these studies had conflicting findings. Although 1 study observed retinal arteriolar narrowing in association with incident chronic kidney disease,[36] another found both retinal arteriolar narrowing and increased venular diameter were associated with incident chronic kidney disease.[37] Other studies, however, did not find associations with chronic kidney disease[38,39] nor decline in renal function.[40]

Limitations of Fundus Photographs

Although the nonmydriatic fundus camera allows the larger-scale application, the predictive value of mild hypertensive retinopathy for end-organ damage in hypertension remains modest (Table 1). In the search for methods to detect subclinical retinopathy damage early, the color fundus photography with advanced software to analyze the retina vessels seems to be more useful.[41] However, fundus photographs remain limited to the larger vessels of the superficial layers of the retinal circulation, namely the arteries and veins. It does not allow the assessment of smaller vessels, ie, capillaries or deep retinal vascular layer and the choroid.

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY

The optical coherence tomography angiography (OCTA) is a functional extension of optical coherence tomography (OCT) which images the retinal vasculature by detecting the movement of red blood cells within the vessels. By comparing repeated OCT *B* scans, it is possible to image the vessels by computing differences among the scans. It has provided us with high-resolution, depth-resolved images of both the superficial and deep retinal vascular layer and the choroid (Fig. 2). The OCTA is also highly attractive for use in large cohort studies and for consecutive follow-up visits as it does not require the administration of intravenous dye.[42] A recent meta-analysis by our group reviewed the studies on quantitative OCTA parameters in hypertensive patients and concluded that certain OCTA parameters could provide objective information about preclinical microvascular changes from systemic hypertension.[43]

Potential Biomarkers Obtained From Optical Coherence Tomography Angiography

The vessel density of the superficial capillary plexus (SVD), vessel density of the deep capillary plexus (DVD), and superficial foveal avascular zone (FAZ) are OCTA parameters that have been extensively explored in hypertension studies. However, as OCTA measures blood flow by motion contrast, the decrease in vessel density in the retinal and/or choroidal capillaries could be due to a low rate of blood flow or capillary occlusions. Therefore, OCTA can only provide quantitative measurements of vessels with rate of blood flow exceeding minimum detection threshold, and measurements generated may not reflect the true extension of vessels.

In the SVD (Fig. 3), Hua and coworkers[44] showed that hypertensive patients with poor blood pressure control had significantly lower SVD as compared to healthy controls. In addition, 2 studies[45,46] showed that the SVD of hypertensive patients of at least 5 years' duration had lower measurements when

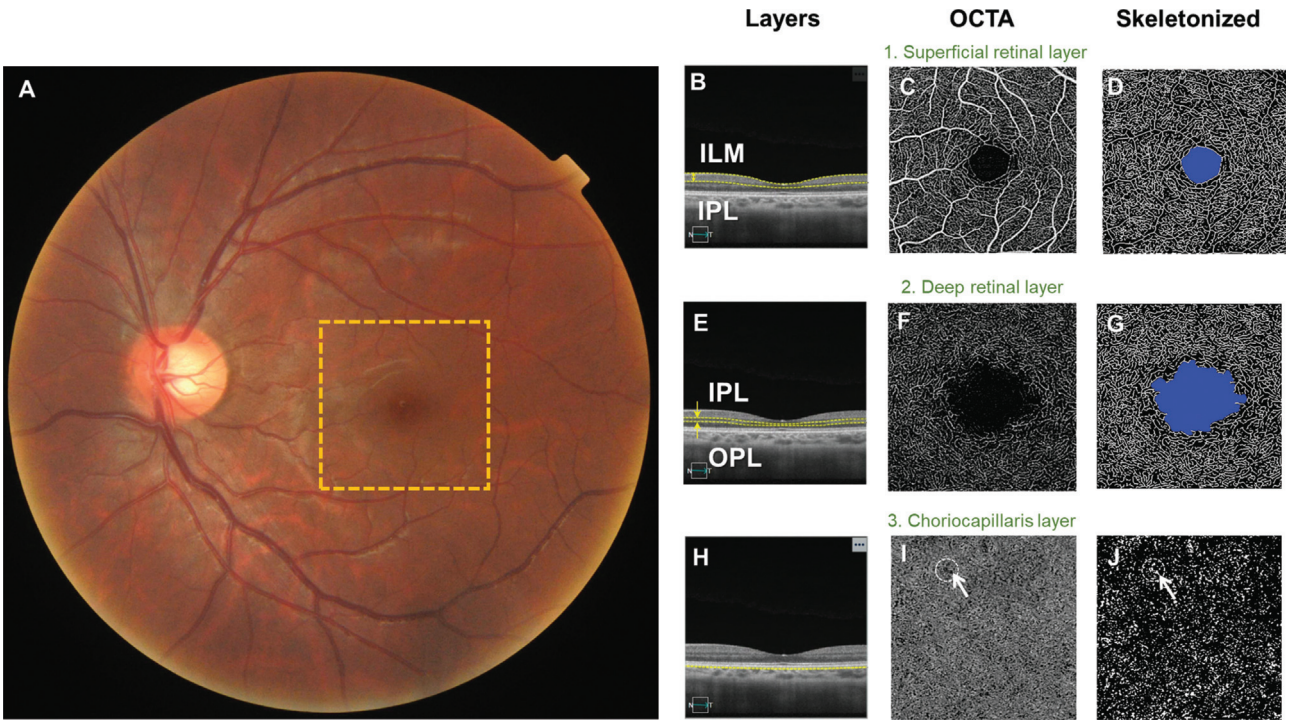

Figure 2. Clinical and optical coherence tomography angiography (OCTA; 3 x 3 mm area; PLEX Elite 9000, Carl Zeiss Meditec) imaging of the left eye. A, Color fundus photograph showing a normal eye. B-D, Images of superficial retinal layer. E-G, Deep retinal layer. H–J, Choriocapillaris layer. OCTA images of the respective plexuses were exported from the review software (B, E, and H), and retinal capillary density and choriocapillaris flow deficits parameters were automatically extracted using a customized MATLAB algorithm (The MathWorks, Inc, Natick, MA; Version R2020b). Foveal avascular zone area demarcated in blue (D and G). The white arrows in I and J indicate the presence of a single flow deficit, which appeared as black in the OCTA image (I), and white in the processed images (J). OCTA indicates optical coherence tomography angiography.

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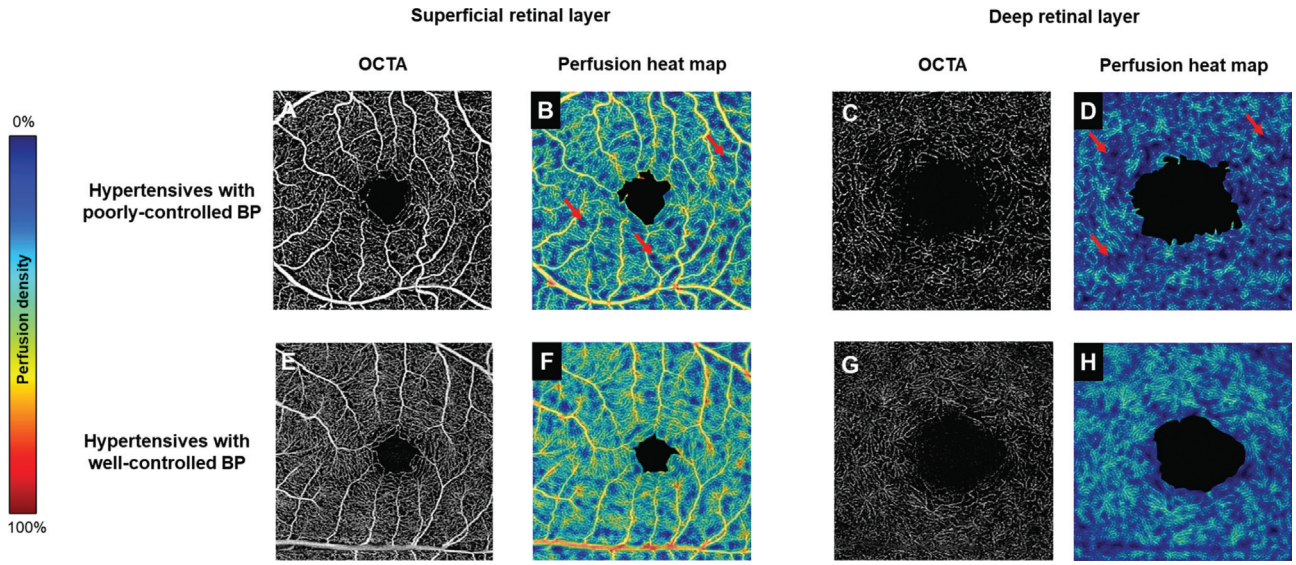

Figure 3. Retinal capillary density maps of the macular region showing the superficial retinal microvasculature of hypertensive patients (A-D) with poorly-controlled blood pressure (BP) and (E-H) with well-controlled BP. Hypertensive patients with poorly-controlled BP generally have sparser capillary density at the superficial (B; 18.02 mm^{-1}) and deep (D; 13.19 mm^{-1}) layers as compared to patients with well-controlled BP who have denser capillaries at the superficial (F; 22.62 mm^{-1}) and deep (H; 18.98 mm^{-1}) layers. The perfusion heat map further indicates the presence of large nonperfused areas (marked by red arrows) that tend to be seen in patients with poorly-controlled BP (B and D) as compared to patients with well-controlled BP (F and H). Foveal avascular zone area (in black) was excluded from the calculation of capillary density.

compared to controls, whereas Peng and coworkers[47] found that the SVD was significantly decreased in patients with hypertensive retinopathy when compared to controls. Several studies, on the other hand,[48,49] did not find a significant difference in SVD between the eyes of hypertensives and controls.

As for the DVD (Fig. 3), several studies[48–50] found that the DVD was significantly reduced in the macula of hypertensive eyes. In addition, Peng and coworkers[4] found that the DVD was reduced in hypertensive patients when compared to controls, independent of the presence of hypertensive retinopathy. However, Hua and coworkers[46] found that there was no difference in DVD between hypertensive patients of least 5 years' duration and controls.

In the FAZ, Donati and coworkers[48] observed a significant increase in the FAZ area in hypertensive patients compared to healthy subjects. Two studies[46,51] found that the FAZ area was significantly larger in patients with more than 10 years of hypertension when compared to controls. Similarly, Lim and coworkers[45] observed that the FAZ area was significantly greater in patients with more than 5 years of hypertension when compared to controls.

Several additional OCTA parameters have been explored, such as fractal dimension and peripapillary vessel calibers. For example, Xu and coworkers[50] observed that the fractal dimension of the retinal capillary plexuses was significantly reduced in the macula of hypertensive eyes. Meanwhile, hypertensive eyes had marginally narrower peripapillary arteriolar caliber.[50]

Other emerging OCTA biomarkers would be the choriocapillaris (Fig. 4), especially with the advent ofswept-source OCTA which offers distinct advantages over the previous spectral-domain OCTA technology, allowing researchers to view the choriocapillaris region underneath the retinal pigment epithelium with much greater clarity. Using the swept-source OCTA, Chua and coworkers[52] reported that in normal controls there were many small choriocapillaris flow deficits, whereas in uncontrolled hypertension there was a progressive reduction in the number of choriocapillaris flow deficits with an increasing mean area of choriocapillaris flow deficits. In addition, the study observed that individuals with uncontrolled systemic hypertension had the most significant choriocapillaris flow deficits compared to well-controlled hypertensives and normal controls.

OCTA parameters may have the potential to create new hypertensive retinopathy classification systems. A recent study by Liu and coworkers[53] proposed a novel 3-stage hypertensive retinopathy classification system using parameters assessed on OCTA, in place of the classic Keith-Wagener-Barker

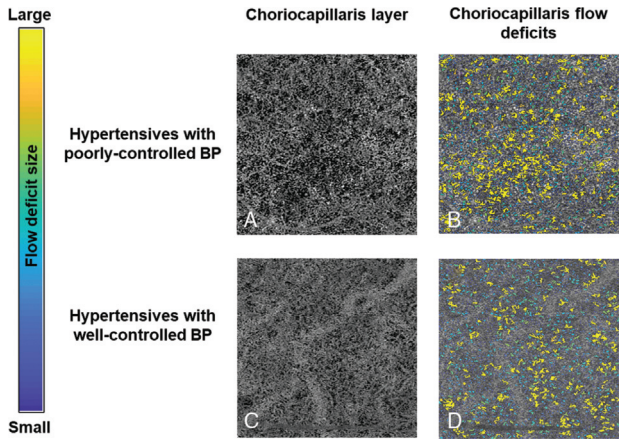

Figure 4. Swept-source optical coherence tomography angiography (3 x 3 mm area) and color-coded maps indicating regions of flow deficits (B; color-coded) of a choriocapillaris layer of a hypertensive with poorly-controlled blood pressure (BP) (A and B) and a hypertensive with well-controlled BP (C and D). The color-coded maps show the presence of larger-sized choriocapillaris flow deficits in a hypertensive with poorly controlled BP (B; labeled as yellow). The presence of flow deficits can be seen as areas of dark regions in the angiogram (A and C) and its sizes are color-coded (B and D).

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classification system. The OCTA classification system was found to have correlations with renal damage but was unable to find a correlation between the stages of the OCTA classification system proposed and cardiovascular events. Whilst novel, the correlation between the proposed classification system and renal damage was cross-sectional in nature, and not appropriate for prognostication. Future studies or meta-analyses can consider using long-term follow-up studies to develop classification systems that have prognostic ability; such systems may have greater clinical utility.

Effect of Antihypertensive Medications Using Optical Coherence Tomography Angiography

Blood pressure levels have been found to be correlated with several OCTA parameters. Xu and coworkers[50] observed that the skeletal and vessel density of the DVD was correlated negatively with mean arterial pressure, and Hua and coworkers[44] observed that blood pressure was significantly correlated with the SVD, DVD, and the inside disc capillary density. Similarly, Peng and coworkers[47] showed that blood pressure was found to be correlated with DVD. In addition, Chua and coworkers[52] showed that choriocapillaris flow deficits were highly dependent on blood pressure control and less on systemic hypertension status, as flow patterns were similar between persons with well-controlled systemic hypertension and healthy controls. This is consistent with the findings of Hua and coworkers[44] that the SVD did not significantly differ between patients with well-controlled blood pressure of more than 10 years and patients with well-controlled blood pressure of 5 to 10 years, suggesting that having a good blood pressure control maintained the structural integrity of the microvasculature in the SVD. Taken together, these findings support the possible beneficial role of blood pressure control in preventing, maintaining, or reversing these preclinical microvascular changes.

Furthermore, it has been proposed that different classes of antihypertensive treatments have differing effects at the microvascular levels.[54] OCTA thus offers the opportunity to observe these effects at the microvascular level noninvasively, and the insights could possibly change practice patterns in terms of medication prescription for different subgroups of patients. For example, Peng and coworkers[47] reported that patients under monotherapies were shown to have lower SVD than patients taking angiotensin-converting enzyme inhibitors (ACE inhibitors or ACE-I)/angiotensin receptor blocker and calcium channel blocker combination therapy, and patients taking only calcium channel blocker had significantly lower DVD. In addition, analyzing digitized red-free monochrome images of fundus photographs, Hughes and coworkers[55] reported that amlodipine- and lisinopril-based treatment was significantly associated with the reduction of arteriolar narrowing. Similarly, Thom and coworkers[56] observed using fundus photography that amlodipine-based treatment was associated with a lesser arteriolar narrowing than atenolol-based treatment. OCTA imaging may give greater insights into these findings and would be an interesting area to explore.

Use of Optical Coherence Tomography Angiography for End-Organ Disease Prognostication

Several studies have explored the association of OCTA parameters and hypertensive end-organ damage in the kidneys and brain. With regards to the kidneys, 5 studies[48,52,53,57,58] have described relationships between OCTA parameters and impaired kidney function based on microalbuminuria and estimated glomerular filtration rate levels. Although both studies reported a reduced retinal capillary density and lower estimated glomerular filtration rate in persons with systemic hypertension, Chua and coworkers[58] reported a change in the superficial vascular layer, whereas Frost and coworkers[57] reported changes in the deep retinal vascular layer. In contrast, however, Donati and coworkers[48] reported that microalbuminuria levels were not significantly correlated with SVD, DVD, or FAZ. In the choriocapillaris, Chua and coworkers[52] showed that changes in the choriocapillaris microvasculature were associated with kidney function. As for the brain and cognition, Wang and coworkers[59] observed a significant decrease in SVD in patients with cerebral small vessel disease, and that the hypoperfusion was associated with cerebral magnetic resonance imaging markers and cognitive function. Future longitudinal research is required to establish whether OCTA metrics improve end-organ disease prognostication over existing markers, or provide an easier method compared to less accessible or more costly tests.

Limitations of Optical Coherence Tomography Angiography Studies

There have been inconsistencies on whether OCTA parameters significantly differ between hypertensive patients and healthy controls. Several reasons explain the discordant findings. First, the small sample size, ranging from 28[60] to 169[47] hypertensive patients without the considerations of relevant confounders. Second, published OCTA studies in hypertensive patients relied primarily on classifications of brachial blood pressures of which targets remain controversial. In recent years, more reliable markers such as fibrosis to monitor the progression of hypertension have been proposed.[61,62] The associations of these new hypertensive markers with OCTA parameters have not been investigated. Lastly, eyes with pathology, such as hypertensive retinopathy, can significantly alter retinal anatomy and cause algorithms to misidentify boundaries. Mislabeling of retinal layers and consequent vessel density measurement error have been reported even in one-third of healthy eyes,[63] and of all the published studies, only the studies by Xu[50] and Donati[48] checked for segmentation errors.

ADAPTIVE OPTICS IMAGING

Several authors have been interested in the pathogenic mechanisms of hypertension, such as the influence of microvasculature changes in early life,[64] or genetic determinants of microvascular structure and function in hypertension.[65] A major challenge is examining early or subtle changes in vascular development as determined by genetic or environmental factors, and how such changes could lead to sustained hypertension in adulthood. For this reason, imaging microscopic features of the retinal vasculature using AO systems could prove useful in such studies.

The application of AO transforms an ophthalmoscope into a microscope, allowing greater in vivo resolution of the retinal microvasculature to an extent that is not possible with conventional clinical imaging modalities.[66] The AO imaging technology uses deformable mirrors to compensate for the optical

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imperfections, also known as aberrations in the eye,[67] allowing retinal vessels to be imaged at near histological levels.[68] Given the remodeling of arterioles may be an early process underlying end-organ damage due to hypertension,[69] the noninvasive nature of AO imaging makes it highly attractive for follow-up studies on pathogenic mechanisms and therapeutic interventions in hypertension.

The AO ophthalmoscopy can be performed using 2 modalities, either the AO flood illumination (AO-FIO) or AO scanning laser (AO-SLO). The AO-FIO system is a fundus photography system at its core, integrated with AO hardware to counteract the optical aberration. It adopts widefield (or flood) illumination and an area sensor to capture a 2-dimensional en face image in 1 single shot. On the contrary, the AO-SLO system is essentially a confocal scanning system where the incident light is tightly focused on 1 spot of the retina, with the help of the AO hardware, and the backscattered light is collected by a single-pixel detector through a confocal pinhole. A 2-dimensional en face image is created when the incident light is raster-scanned over the retina. Compared to AO-SLO, the AO-FIO systems are inherently less susceptible to motion artifacts owing to their fast acquisition speed. However, without the confocal pinhole to reject the out-of-focus signals, AO-SLO produces images with less signal-to-noise ratio.[70] This review will focus on AO-FIO as more studies are published. The AO-SLO systems were mainly custom built[71] and have only been made commercial recently.

Potential Biomarkers Obtained From Adaptive Optics Imaging

A series of vascular biomarkers such as the inner diameter, the outer diameter, and the parietal thickness can be imaged using the AO-FIO (Fig. 5). These biomarkers are commonly measured in arterioles because the venule wall is often not visible on AO-FIO images (Fig. 5). In a recent meta-analysis, Bakker et al[71] summarized the results of studies included in PubMed and Scopus databases as of July 9, 2020, on retinal biomarkers obtained from AO imaging in patients with hypertension. They concluded that a significantly smaller inner diameter[3,68,72–74] (Fig. 6) and larger parietal thickness[3,68,72,73] can be observed in hypertensive patients as compared to healthy controls, resulting in an increased wall-to-lumen ratio[3,68,72,73,75] without an increase in wall cross-sectional area.[3,68,72–76] This finding supports the prevailing theory of arteriolar remodeling in hypertension[77] with microscopic level scrutiny. Their overall conclusion from this systematic review is that although the AO vascular biomarkers are altered in patients with hypertension, there is a need to standardize the AO imaging protocols and validate these procedures for the longitudinal monitoring of hypertension.

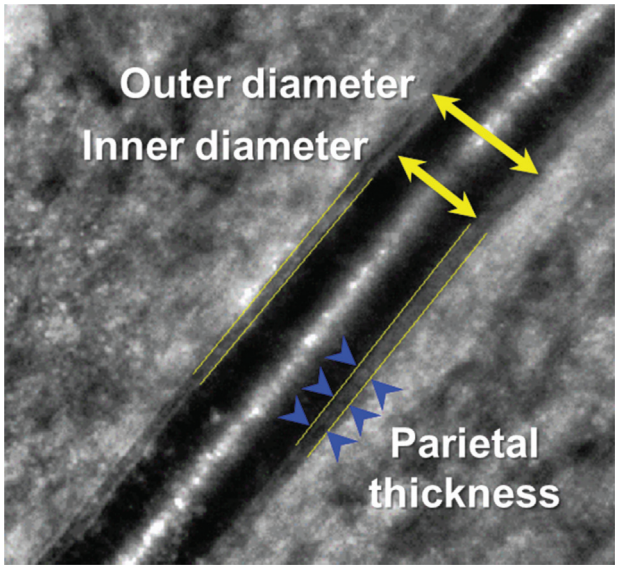

Figure 5. Vascular imaging biomarkers as imaged from the adaptive optics image (RTX1, Imagine Eyes, France).

Effect of Antihypertensive Medications Using Adaptive Optics Imaging

Several AO studies have observed that blood pressure management in hypertension can lead to the reversal of retinal microvascular changes.[73,78] For instance, a significant increase was observed in inner diameter and reduction in parietal thickness after antihypertensive treatment,[78] suggesting a reversal of eutrophic remodeling as a result of blood pressure changes. With regards to specific medication classes, however, AO imaging studies have presented discordant findings. Gallo and coworkers[74] found no significant difference between the effects of different classes of antihypertensive treatment on retinal microvascular remodeling, whereas a multivariate analysis by Rosenbaum and coworkers[73] showed that hypertension drug regimen was not an independent predictor of any retinal anatomical indices. In contrast, De Ciuceis and coworkers[79] found a significant reduction in the wall-to-lumen ratio of hypertensive patients after undergoing combined lercanidipine and enalapril treatments over a period of 24 weeks.

Use of Adaptive Optics Imaging for End-Organ Disease Prognostication

The wall-to-lumen ratio of retinal arterioles has shown a strong correlation with the media-to-lumen ratio of subcutaneous vessels,[3] a potent predictor of cardiovascular and cerebrovascular events in multivariate analyses[80] but which requires invasive biopsy of gluteal tissue for analysis. There is currently, however, a paucity of studies examining the relationship between AO imaging biomarkers and end-organ damage in hypertensive cohorts. The only study to do so thus far failed to demonstrate a significant relationship between the wall-to-lumen ratio of patients with and other meaningful end-organ injuries.[81] It was however a small study of 27 patients and only included patients with malignant hypertension.

Limitations of Adaptive Optics Imaging

Despite its capability to capture high-resolution images of the retinal vasculature, AO imaging is not quite ready for routine clinical care. This is because it is tedious to capture AO images and can be exhausting for patients. Furthermore, as the region of analysis in AO imaging is often limited to a single vessel in a limited field of view, usually a segment of the superotemporal arterioles,[3,68,73–75,79] it is difficult to be certain that the changes in that arteriole are reflective of all other retinal vessels. In the future, large field-of-view montages may be attractive and will potentially yield more reliable information on the microcirculatory status.

Moreover, the optics of the AO imaging is highly sensitive to media opacities, fixation stability, and tear film quality. Likewise, image processing, montaging, and analysis require custom

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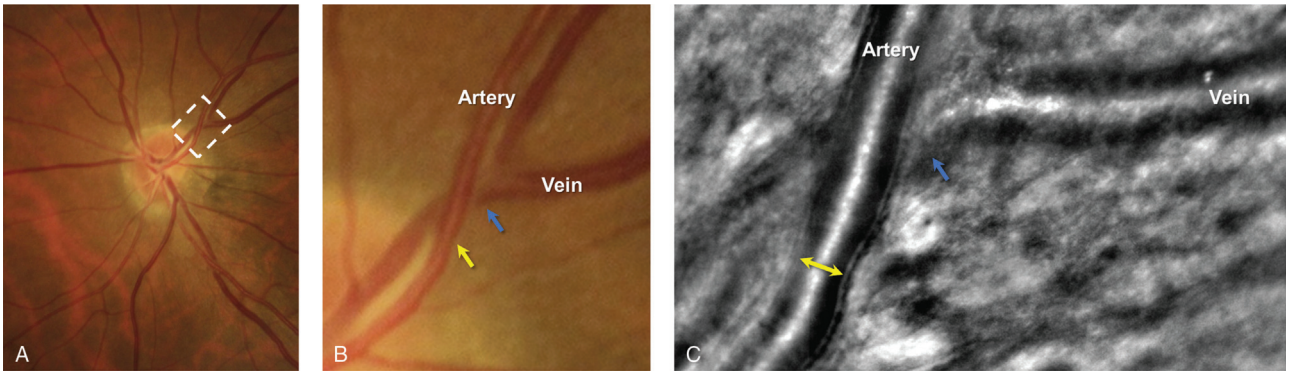

Figure 6. In an eye with mild hypertensive retinopathy, comparing fundus photographs (A and B) and adaptive optics image (RTX1, Imagine Eyes, France) showing arteriovenous nicking (blue arrow) with focal arteriolar narrowing (yellow arrow) (C).

software and technical expertise due to the lack of automated techniques. Technological imaging advances in speed, tracking, and software improvement will improve the scan quality in challenging eyes and produce reports quickly in a fast-paced clinical setting.

In addition, the magnification of vessels on AO imaging is dependent on the axial length of the eye being imag ed.[82] Specifically, measurements that rely on absolute values, such as the inner diameter and outer diameter, are impacted by the magnification effect of the eye and can cause bias when comparing values between subjects; however, parameters that compute a dimensionless ratio, such as the wall-to-lumen ratio, are not affected by this issue.

FUTURE DIRECTIONS

The advent of deep learning using artificial intelligence creates exciting possibilities for the future of hypertension diagnosis, cardiovascular risk factor screening, and prediction of cardiovascular events.[83] Artificial intelligence has the potential to predict the presence of hypertension using fundus photographs. For instance, several models developed have achieved an area under the curve of 0.65 to 0.77 and an accuracy of 60.9% to 68.8% in predicting hypertension in different populations living in China.[84,85] These models may be especially useful in detecting patients with white coat hypertension (higher blood pressure readings at the doctor's office than other settings) or masked hypertension (normal blood pressure readings at doctor's but chronically high blood pressure outside of the clinic). Deep learning may allow clinicians to rapidly and noninvasively detect these underdiagnosed groups of patients and give them the appropriate treatment that they would otherwise not receive.

Apart from predicting hypertension status, Google researchers Poplin and coworkers[86] showed using White and Hispanic populations that using deep learning on retinal images alone was sufficient to predict several cardiovascular risk factors including age, gender, smoking status, blood pressure, and body mass index. The same deep learning algorithm was also able to predict the onset of major adverse cardiovascular events within 5 years. Similarly, using more than 70,000 images from multiple countries and multiple ethnicities, Cheung and coworkers[87] developed a deep learning model that could predict multiple cardiovascular risk factors from retinal vessel calibers. Lastly, Rim and coworkers[88] developed a deep learning model demonstrating superior performance in predicting the presence of coronary artery calcium, a preclinical marker of atherosclerosis that is strongly associated with risk of clinical cardiovascular disease.[89] The use of deep learning is exciting as it can help make cardiovascular risk screening of a large population both technically and economically feasible.

CONCLUSIONS

Since the late 19th century, the significance of retinopathy signs as indicators of systemic morbidity and mortality has long been recognized. Furthermore, performing ophthalmologic examinations in patients with hypertension has been endorsed by international hypertension management guidelines.[90,91] However, retinal assessment nearly disappeared from routine clinical practice towards the end of the 20th century.

Major technological advances in ocular imaging techniques have improved the way the retinal microcirculation can be assessed, offering a unique opportunity to further our understanding of eye–body relationships and support the development of novel diagnostic and prognostic tools through noninvasive means. Furthermore, microvascular imaging techniques such as the OCTA can be deployed in community primary care settings to identify people at risk of systemic diseases and follow their progression during treatment. This setting allows the collection of large data sets for the study of "Oculomics," the association of ophthalmic biomarkers with systemic health and disease.[92] Such microvascular damage, if demonstrable, may provide a biomarker of at–risk individuals with the greatest likelihood for progressive cardiac, neurological, and renal function decline.

In summary, although the clinical and prognostic value of early microvascular retinal abnormalities assessed either by OCTA and AO imaging remains lacking, the availability of novel standardized quantitative imaging analysis techniques may shed new insights on the challenging task of identifying hypertensive individuals at risk of end–organ damage. Furthermore, the combination of deep learning with OCTA and AO imaging techniques could help provide better risk stratification of hypertensive patients.

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