Retinal Microvasculature as a Model to Study the Manifestations of Hypertension

Carol Yim-lui Cheung, M. Kamran Ikram, Charumathi Sabanayagam, Tien Yin Wong

Abstract—The retinal vasculature allows direct noninvasive visualization of the body’s microvasculature. Because the retina and other end organs (brain and kidney) share similar anatomic features and physiological properties, the retinal vessels offer a unique and easily accessible window to study the health and disease of the human microcirculation. Advanced retinal vascular imaging technologies have been developed to allow a more objective and precise assessment of retinal vascular changes. The changes in the retinal vasculature associated with hypertension can be broadly divided into 3 groups: (1) classic retinal vascular changes in response to blood pressure (referred to as hypertensive retinopathy signs), (2) changes in retinal vascular caliber, and (3) changes in more global geometrical patterns of the retina. In this review, we summarize the current understanding of the relationship between retinal vascular changes and blood pressure, the evidence for the retinal vasculature as a biological model to study the manifestation and early pathogenic correlates of hypertension, the latest advances in retinal vascular imaging technologies, and the future opportunities and challenges of retinal vascular imaging. We suggest that further development of retinal vascular analyses and standardized measurement protocols, evaluation of the clinical use of retinal vascular imaging in assessing cardiovascular risk prediction, and using retinal vascular imaging to test antihypertensive treatments will allow the translation of retinal vascular imaging as a tool to improve the diagnosis, prognosis, and management of hypertension in clinical practice. (Hypertension. 2012;60:1094-1103.) ● Online Data Supplement

Key Words: clinical science ▪ microcirculation ▪ microvasculature ▪ retina ▪ retinal vascular imaging

Hypertension has profound effects on both the structure and function of the microvasculature.1,2 The presence of small vessel disease, specifically vasoconstriction, rarefaction, and narrowing of the peripheral small arteries and arterioles, is thought to be a key pathological characteristic of hypertension. These microvascular changes, in turn, have been linked to target end-organ damage (TOD), such as cardiovascular disease (CVD), stroke, left ventricular failure, and nephropathy seen in hypertension.3−5 Concurrently, changes in the microvasculature related to increasing peripheral vascular resistance have also been suggested to play a key role in the development and pathogenesis of hypertension.6,7

Despite the importance of the microcirculation as both a means to study the manifestations and early pathogenic correlates of hypertension, most previous works have been based on animal models, in vitro experiments, and small clinical studies.1,8,9 This is largely because it is technically challenging to conduct in vivo clinical studies on the microcirculation.3,10

Because the retina and other end organs (brain and kidney) share similar anatomic features and physiological properties (eg, nonanastomotic end arteries, blood-brain, blood-kidney, and blood-retina barrier), the retinal vessels, measuring 100 to 300 µm in size, offer a unique and easily accessible window to study the health and disease of the human microcirculation.11 Although this concept is well known,12 it is only with the introduction of digital retinal photography in the last 2 decades that retinal vascular changes could be objectively measured and monitored in a precise manner.

Retinal vascular changes-associated hypertension can be broadly divided into 3 groups: (1) classical retinal signs in response to blood pressure (BP) (referred to as hypertensive retinopathy signs), (2) changes in retinal vascular caliber (a new area of research with quantitative measurement of retinal caliber that has generated considerable interest), and (3) changes in more global geometrical retinal vascular patterns (an emerging research area).

In this review, we summarize current understanding of the relationship between retinal vascular changes and BP, the latest advances in retinal vascular imaging technologies, and the future opportunities and challenges.
Relationship of Retinal Vascular Changes to BP

Classic Clinical Effects of Hypertension on the Eye

Hypertensive retinopathy refers to changes in the retina in response to elevated BP. Similar changes in the choroidal and optic nerve circulations are referred to as hypertensive choroidopathy and hypertensive optic neuropathy, respectively. Of the 3, hypertensive retinopathy is by far the most common manifestation and appears earlier and at milder stages of hypertension than choroidopathy and optic neuropathy.

Hypertensive retinopathy is broadly divided into different stages, including vasoconstrictive, sclerotic, exudative, and malignant hypertension phases. These phases are not always sequential. For example, in patients with acutely raised BP, signs of retinopathy reflecting the exudative stage (eg, retinal hemorrhage) may be present without features of the sclerotic stage (eg, arteriovenous nicking). In fact, hypertensive retinopathy signs are detected frequently in persons without a known history of hypertension.

There have been many different classifications for hypertensive retinopathy. Traditionally, the Keith-Wagener-Baker system classifies patients with hypertension into 4 groups of increasing severity. A simplified classification of hypertensive retinopathy based on prognosis of different signs from recent population-based data has been proposed (Table S1 in the online-only Data Supplement).

Measurement of Retinal Vascular Caliber

To document generalized retinal arteriolar narrowing, one of the early signs of hypertensive retinopathy, computer software was designed to measure retinal vessel caliber in an objective manner. The most widely used program was first developed in the Atherosclerosis Risk in Communities (ARIC) Study, in which retinal vascular caliber was measured within a zone 0.5 to 1.0 disc diameter away from the optic disc margin. Such methods can allow measurements of retinal vessel widths (caliber or diameter) to quantify generalized arteriolar narrowing objectively and reliably (Figure S3A in the online-only Data Supplement) and therefore improve the sensitivity and specificity in detecting retinal microcirculatory alterations. Table 1 shows the parameters for measurement of retinal vascular caliber from retinal photographs using computer-assisted methods in clinical research.

Recent epidemiological studies using such methods have shown that changes in retinal vascular caliber are associated with a range of systemic factors. The associations between retinal vascular caliber and BP (concurrent, past, and future), TOD, and CVD in general population-based studies are summarized (Table S2). Such associations remain statistically significant even after multivariate adjustment for other cardiovascular factors. These studies provide strong evidence that retinal vascular caliber measurement can be used as a research tool to better understand the relationship between the retinal microvasculature and systemic diseases and also potentially used in clinical practice for retinal assessment.

Nevertheless, the measurement of retinal vascular caliber from photographs largely reflects the width of the red blood cell column (ie, internal lumen diameter), and it does not capture vessel wall because the wall is transparent to light. The variation attributed to cardiac cycle is also a matter of concern. Finally, specialized computer software and trained technicians are required for such measurements and, thus, not yet widely available for clinical use.

Table 1. Parameters for Measurement of Retinal Vascular Caliber From Retinal Photographs Using Computer-Assisted Methods in Clinical Research

<table>
<thead>
<tr>
<th>Retinal Vascular Parameters</th>
<th>Interpretation</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriovenous ratio</td>
<td>Ratio of the caliber of arterioles to venules</td>
<td>Dimensionless, controls for magnification differences from camera lenses and refractive error</td>
<td>Nonspecific. Changes in arteriovenous may reflect changes in arteriolar or venular diameter or both</td>
</tr>
<tr>
<td>Central retinal artery equivalent</td>
<td>A summary index reflecting the average width of retinal arterioles</td>
<td>Reflects distinct systemic vascular disease pathways that tend to target the arterial system</td>
<td>Only measures the width of the reflective erythrocyte column and may underestimate the true internal vessel diameter</td>
</tr>
<tr>
<td>Central retinal vein equivalent</td>
<td>A summary index reflecting the average width of retinal venules</td>
<td>Reflects distinct systemic vascular disease pathways that tend to target the venous system</td>
<td>Only measures the width of the reflective erythrocyte column and may underestimate the true internal vessel diameter</td>
</tr>
</tbody>
</table>
the associations among retinal venular widening, BP, and hypertensive complications are not entirely clear.

**Retinal Vascular Changes and Past BP**

More interesting than concurrent BP, there is recognition that the patterns of specific retinal vascular changes vary with current and past BP levels. Generalized retinal arteriolar narrowing and arteriovenous nicking, for example, are related not only to current BP levels but also to BP levels measured in the past, suggesting that these 2 retinal signs reflect the cumulative effects of long-standing hypertension and are persistent markers of chronic hypertensive damage. In contrast, focal arteriolar narrowing, retinal hemorrhages, microaneurysms, and cotton wool spots are related only to concurrently measured BP that mirror the effects of momentary BP changes (ie, a transient effect). Nonetheless, the rate of transition for the retinal vascular changes in relation to increase in BP remains to be determined.

**Retinal Vascular Changes and Other Forms of BP**

Ambulatory BP has better correlation with TOD and CVD outcomes than clinic BP in the general population, as well as in hypertensive patients. However, there is lack of data yet to show changes in retinal vasculature with ambulatory BP and the hemodynamic load over the 24-hour period. Furthermore, there are no good data on retinal vascular changes in relation to variability of BP, central BP, and other common clinical hypertension phenotypes (eg, masked and white-coat hypertension).

**Retinal Vascular Changes as a Model to Study Manifestations of Hypertension**

**Stroke**

**Relationship With Clinical Stroke**

Numerous large population-based studies have reported the strong link between retinal vascular changes and clinical stroke. The ARIC Study initially showed that persons with retinal vascular changes at baseline were more likely to develop an incident clinical stroke. The ARIC Study further demonstrated that persons who had both cerebral magnetic resonance imaging lesions and retinopathy signs were at substantially higher risk of incident clinical stroke than those without either abnormality. Subsequent studies consistently reported that persons with retinal vascular changes at baseline were more likely to develop stroke even after controlling for traditional risk factors. Importantly, a recent meta-analysis confirmed that wider retinal venular caliber, rather than narrower arteriolar caliber, is related to risk of stroke, which provides evidence that venules may play a key role in pathogenesis of microvascular stroke.

Some recent studies further demonstrated that retinal vascular changes may allow further refinement and subtyping of stroke. In a multicenter study of patients with acute stroke, different hypertensive retinopathy signs were associated with specific stroke subtypes. For example, retinal arteriolar narrowing was associated with lacunar stroke, whereas retinal hemorrhages were linked with cerebral hemorrhages. These findings suggest that retinal vascular changes reflect specific cerebral microvasculopathy and may further help to understand the underlying pathologic mechanisms.

**Relationship With Subclinical Stroke**

In addition, it is increasingly evident that retinal vascular changes are associated with subclinical cerebral changes. For example, in the ARIC Study, middle-aged, generally healthy, persons with retinal vascular changes were more likely to have subclinical magnetic resonance imaging–defined cerebral infarction and cerebral white matter lesions than those without these signs. Recent prospective data from the ARIC Study further showed that retinal vascular changes are associated with incident cerebral atrophy, incident cerebral infarct, incident lacunar infarct, and white matter lesion incidence and progression, independent of traditional risk factors. These data provide strong evidence that retinal vascular changes are associated with subclinical cerebral changes.

**Table 2. Studies of the Association Between Novel Retinal Vascular Measures (Tortuosity, Fractals, Branching Angles) From Retinal Fundus Photography With Blood Pressure (Concurrent, Past, Future), Target End-Organ Damage, and Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Novel Retinal Vascular Parameters</th>
<th>Changes in Parameters</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tortuosity</td>
<td>Retinal arteriolar tortuosity</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Retinal venular tortuosity</td>
<td>Increased</td>
</tr>
<tr>
<td>Fractal dimension</td>
<td>Retinal vascular fractal dimension</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased</td>
</tr>
<tr>
<td>Bifurcation</td>
<td>Retinal arteriolar branching angle</td>
<td>Decreased</td>
</tr>
<tr>
<td></td>
<td>Retinal arteriolar branching asymmetry ratio</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Retinal arteriolar length:diameter ratio</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Retinal arteriolar branching coefficient (optimality ratio)</td>
<td>Increased</td>
</tr>
<tr>
<td></td>
<td>Retinal arteriolar optimality parameter (deviation of junction exponent)</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Furthermore, these data mirror the effects of momentary BP changes.
changes mirror preclinical structural changes in the cerebral microcirculation and support the hypothesis that retinal microvascular changes provide insights into the microvascular structure and function in the cerebral microcirculation.

Coronary Artery Disease and Heart Failure
There is also evidence that retinal vascular changes are predictive of clinical coronary artery disease events; however, the results of these studies show less consistent associations than with stroke. A meta-analysis of 6 population-based studies provides robust evidence to confirm that retinal vascular caliber is associated with an increased risk of coronary artery disease in women but not in men. Furthermore, in the ARIC Study, persons with retinopathy were 3 times more likely to develop congestive heart failure than those without retinopathy, whereas controlling for the presence of other cardiovascular risk factors. Nevertheless, the incremental predictive ability over that of the Framingham model was only modest.

Renal Disease
Animal studies showed pathological changes in the retinal and renal microcirculation are correlated in spontaneously hypertensive rats. The significance of hypertensive retinopathy signs as risk indicators has long been recognized in humans with renal disease. Retinal vascular changes assessed by standardized photographic methods were demonstrated to be associated with microalbuminuria and renal impairment in cross-sectional studies. Such association was independent of BP, diabetes mellitus, and other risk factors and was also seen in persons without diabetes mellitus or hypertension. However, the findings from prospective studies are mixed. Retinal arteriolar narrowing was associated with chronic kidney disease among whites in the Multi-Ethnic Study of Atherosclerosis and with 6-year change in serum creatinine among the ARIC population, whereas no association was found among elderly adults in the Cardiovascular Health Study and elderly whites in the Beaver Dam Eye Study.

CVD Mortality
Retinal vascular changes have also been shown to correlate with increased risk of CVD mortality, stroke mortality, and coronary heart disease mortality. For example, in the Blue Mountains Eye Study, persons with retinopathy signs were more likely to die from coronary heart disease than persons without this sign, with an equivalent risk similar to that of diabetes mellitus. Also, in the Ibaraki Prefectural Health Study with 87,890 individuals, both hypertensive and nonhypertensive subjects with mild retinopathy signs were more likely to die from CVD mortality, independent of traditional cardiovascular risk factors. These data suggest that retinal vascular changes may convey additional prognostic information than other risk measures of CVD.

Pathogenesis of Cardiovascular Events
There is emerging evidence of a significant role of the microcirculation on CVD and TOD. Studies show that alterations in structure and function of small arteries may contribute to CVD and TOD in hypertensive patients. For example, an increased media:lumen ratio of gluteal subcutaneous small arteries (abnormal resistance artery structure) can predict cardiovascular events in essential hypertension. Changes in retinal vasculature (caliber, tortuosity, fractals, bifurcation, and wall:lumen ratio) may reflect similar changes in the systemic peripheral circulation (e.g., vasoconstriction, intimal thickening, and medial hyperplasia), providing insights into the structure and function of small vessels that are important in hypertension and associated TOD and CVD. Recent studies also showed that reduced large artery compliance is associated with narrowed retinal arterioles, independent of age, BP levels, and other cardiovascular risk factors. These studies further support the concept that diminished large-artery compliance is associated with microvascular dysfunction, and thus both small and large (ie, resistive versus compliance) arteries are important in the pathogenesis of CVD and TOD.

Retinal Vascular Changes as a Model to Study Early Correlates of Hypertension
Role of Microcirculation in the Pathogenesis of Hypertension
The microcirculation plays a critical role in the pathophysiology of hypertension. Animal models, in vitro experiments, and clinical studies have demonstrated that microcirculatory changes (e.g., arteriolar narrowing and capillary rarefaction) are linked with the development of hypertension. It is suggested that alterations in the structure and function of the microcirculation are one of the earliest changes in the pathogenesis of hypertension, including impaired vasomotor tone leading to enhanced vasoconstriction or reduced vasodilator responses, anatomic alterations to the structure of individual precapillary resistance vessels, and rarefaction of arterioles or capillaries within a given vascular bed. Investigating the microvascular structure and function in retina may therefore improve the understanding of the pathogenesis of hypertension and related TOD and CVD. The Figure illustrates the contribution of studying retinal vascular changes to the understanding of the pathogenesis of hypertension and related TOD and cardiovascular events.

Retinal Vascular Changes and Future Risk of Hypertension
Retinal Vascular Changes and Risk of Hypertension
Although there were studies that showed that arteriolar narrowing has been found to precede the development of hypertension in rats, as of a decade ago, there were almost no studies that showed that arteriolar narrowing is related to the development of hypertension in humans. There is now good evidence, however, that generalized retinal arteriolar narrowing may precede the development of hypertension in humans. These longitudinal data demonstrate that structural alterations of microvasculature, especially narrowing and vasoconstriction of the small arteries and arterioles, are independently associated with development of hypertension. Furthermore, in some studies, normotensive persons with retinal arteriolar narrowing were more likely to develop hypertension, and those with mild hypertension were more likely to progress to severe stages of hypertension. Thus, generalized retinal arteriolar narrowing, possibly reflecting more widespread systemic
Peripheral vasoconstriction, may be an early preclinical marker of hypertension.

**Retinal Vascular Changes and BP in Children**

Importantly, new studies in children have demonstrated that the association between retinal arteriolar narrowing and elevated BP can be observed even in children as young as 4 to 5 years of age. These findings suggest that the impact of elevated BP on the retinal microcirculation occurs in early life,71–72 which may then track through to adulthood, even before the onset of overt hypertension. Furthermore, the association of parental history of hypertension with narrower retinal arteriolar caliber in young girls aged 6 years73 indicates the need for instituting CVD prevention measures early in life among offspring of hypertensive parents.

**Retinal Vascular Changes and Hypertension Genes**

In addition, recent genetic epidemiology studies have provided clues to new vascular pathophysiological processes linked to changes in retinal vascular caliber. A genome-wide linkage analysis from the Beaver Dam Eye Study demonstrated that retinal arteriolar caliber links to multiple genetic loci, which are associated with regulation of BP, endothelial function, and vasculogenesis,74 suggesting that retinal arteriolar narrowing may be a surrogate marker of an individual’s genetic predisposition to hypertension.75 These findings may allow understanding of the contribution and biological mechanisms of microcirculatory changes that underlie hypertension.

**Advances in the Retinal Vascular Imaging Technologies**

**Assessment of Global Geometrical and Branching Parameters of the Retinal Vasculature**

Previous studies have focused on retinal vascular caliber for quantifying the retinal vascular changes using computeraided methods. The human circulatory system is a branching system that conforms to optimum design principal (Murray principle of minimum work).76 Deviations or alterations from optimal architecture are speculated to result in impaired microcirculatory transport, reduced efficiency, and, thereby, a greater risk of vascular damage.76–78

With innovative technology in retinal photography and computing image processing techniques, new computer-based programs were developed (Figure S3B) to perform objective and quantitative assessment of novel classes of retinal geometrical and branching parameters, such as tortuosity, fractal dimension, branching angles, and vascular length:diameter ratio reliably and rapidly (Figure S3C through S3E in the online-only Data Supplement). Examining the branching pattern of the retinal vasculature may indicate the optimal state of the retinal microcirculation and provide additional cardiovascular risk information to enable better predictive ability of cardiovascular outcomes.

Recent clinical studies showed that these new parameters are related to microvascular damage, such as hypertension,78,79–83 stroke,84–86 CVD mortality,87,88 kidney dysfunction,89,90 and diabetic retinopathy,90–92 suggesting that vascular disease can be detected and monitored by measuring subtle damage from the retinal branching vasculature. Yet, it remains unproven as to whether the deviations cause or correlate with diseases. Table 2 summarizes the associations between the new retinal vascular measures and BP, TOD, and CVD from the clinical studies. In addition to retinal vascular caliber, changes in these new parameters may reflect similar changes in the systemic peripheral, on the level of BP and occurrence of hypertension, and on CVD.

**Assessment of Dynamic Retinal Vascular Changes**

Endothelial dysfunction, characterized by reduced nitric oxide bioavailability, plays a central role in the pathogenesis of vascular diseases, including hypertension. In the retina, nitric oxide seems to play a role in flicker-induced vasodilation of the human retinal vasculature.93 The normal physiological response to stimulation with diffuse luminance flicker is dilatation of retinal vessels mediated by nitric oxide, and this physiological response becomes altered in a variety of pathological states. The dynamic vessel analyzer is a commercially developed system to provide a dynamic analysis of retinal vascular dilatation in response to diffuse illuminance flicker, which is a noninvasive measurement of vascular reactivity in the retinal microcirculation. Recent small sample size studies demonstrated a reduced flicker response in retinal arteriole dilation in hypertension.94,95 These studies suggest that the flicker response of retinal vessel diameter could be a new and noninvasive method for detecting early functional damage (endothelial dysfunction) and may potentially indicate the improved microvascular function under antihypertensive therapy.

**Assessment of Retinal Vascular Flow**

Vascular remodeling of small and large vessels is a characteristic feature in hypertension, resulting in an increase in the media:lumen ratio or wall:lumen ratio of small arteries and arterioles by increasing vascular resistance. Scanning laser Doppler flowmetry with automatic full-field perfusion imaging analysis is another novel approach to enable noninvasive and easily repeatable assessment of retinal arteriolar structure. Such assessment allows quantification of the outer and lumen diameters of the retinal vessels and calculation of wall thickness, wall:lumen ratio, and retinal capillary flow by assessing retinal vessels widths in a dynamic fashion to analyze vascular
remodeling of retinal arterioles in vivo (Figure S4).\textsuperscript{96,97} The test-retest measurements of retinal arteriolar structure using scanning laser Doppler flowmetry has been shown to be reliable.\textsuperscript{98} The validity of the wall:lumen ratio of retinal arterioles has also been assessed by examining the correlation of media:lumen ratio of subcutaneous small arteries with micromyography, providing evidence that retinal arterioles undergo remodeling similar to that seen in arterioles of the subcutaneous tissue.\textsuperscript{99} Using such approach, an increased wall:lumen ratio of retinal arterioles was initially demonstrated in treated hypertensive patients with cerebrovascular event,\textsuperscript{100} as well as in untreated hypertensive patients.\textsuperscript{101} Further recent studies report that increased wall:lumen ratio of retinal arterioles is correlated with increased BP, urinary albumin excretion, and cerebrovascular damage.\textsuperscript{100–103} Compared with assessment of retinal arteriolar narrowing with retinal fundus photography, assessing wall:lumen ratio of retinal arterioles may provide further indication on vascular remodeling, but its prognostic significance has not yet been evaluated in prospective studies, and the technical availability of scanning laser Doppler flowmetry is limited.

**Other New Imaging Tools for Retinal Analysis**

Advanced retinal imaging tools, for example, ultra-widefield retinal imaging, adaptive optics, retinal oximeter, and Doppler optical coherence tomography, have been launched recently to further measure and analyze the structure and function of the retina, including peripheral retinal vasculature, foveal capillary network, retinal oxygen saturation, retinal blood flow, and choroidal vasculature. These new retinal imaging tools are promising to examine the link between eye and hypertension in advance. The prognostic significance of using these new technologies is yet to be evaluated particularly in longitudinal study.

**Unresolved Questions and Future Directions**

**Is a Clinical Retinal Examination Useful for Assessment of Hypertensive Retinopathy?**

The clinical assessment of hypertensive retinopathy signs with the use of an ophthalmoscope has long been regarded as part of the standard evaluation of patients with arterial hypertension.\textsuperscript{15} Nevertheless, high variability of direct fundoscopic examination between observers has been shown, and it has been argued that a routine clinical assessment of quantitative hypertensive retinopathy signs is of limited additional value in the management of patients with hypertension.\textsuperscript{104} Moreover, the evidence of a prognostic impact of early retinal vascular abnormalities on cardiovascular risk stratification is less well established.\textsuperscript{105} However, most international hypertension management guidelines, including the US Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the British Society of Hypertension, the European Society of Hypertension, and the European Society of Cardiology,\textsuperscript{106–108} still emphasize that hypertensive retinopathy, with left ventricular hypertrophy and renal impairment, is an indicator of TOD, and its presence should be an indication for a more aggressive approach in managing these hypertensive patients.\textsuperscript{107}

Digital retinal fundus photography is a potentially sensitive and precise method for assessing retinal vascular changes. Studies showed that the reliability of retinal vascular changes via standardized assessment using digital retinal photography is high.\textsuperscript{109} Moreover, new approaches using computer-assisted programs to quantify retinal vascular changes offer increasingly accurate and repeatable assessment of the retinal vasculature.\textsuperscript{28} Development of standardized photographic methods for the assessment of retinal vascular changes may therefore enable more accurate stratification for cardiovascular risk in patients with hypertension for better management.

**Can Retinal Vascular Imaging Be a Surrogate Measure to Evaluate New Therapeutic Interventions in Hypertension?**

Treatment of hypertension is associated with important reductions in risk of major vascular events including stroke and coronary heart disease. Retinal analysis allows the study of the microcirculation in human hypertension not only with respect to pathophysiological questions but also in relation to new therapies for hypertension. Studies have demonstrated regression of hypertensive retinopathy signs in response to BP reduction and that regression is different in response to different antihypertensive regimens (eg, angiotensin-converting enzyme inhibitors seem to have a more favorable effect on the retinal vasculature).\textsuperscript{109–111} Changes in retinal vasculature, markers of hypertensive state, may act as therapeutic targets capable of reflecting the effectiveness of antihypertensive drug treatment in controlling elevated BP values. Nevertheless, data describing the impact of antihypertensive therapy on retinal vascular changes are still lacking. There needs to be more studies to demonstrate regression of retinal vascular changes via interventions. The potential impact of antihypertensive drug treatment on the patterns of the retinal microcirculation remains unclear. Further prospective controlled trials are required to clarify whether specific reduction of retinal vascular damage also reduces the morbidity and mortality associated with CVD. Moreover, targeting retinal microcirculation to prevent end-organ damage beyond BP reduction is another possible therapeutic strategy in the treatment of hypertension.

**Is Retinal Vascular Imaging Useful as a Tool to Screen for CVD?**

A substantial proportion of CVD is not explained by traditional risk factors alone. Current cardiovascular biomarkers (eg, C-reactive protein) and risk assessment methods (eg, Framingham risk score model) can provide only modest improvements in predictive accuracy.\textsuperscript{112,113} Despite consistent large epidemiological studies demonstrating the relationship between retinal vascular changes and risk of CVD (as reviewed above), retinal vascular imaging is only used as a research tool and not yet as a clinical tool of daily routine. There remains scepticism whether retinal vascular assessment can provide additional prognostic information on cardiovascular risk prediction, in addition to traditional risk factors. Furthermore, no studies have compared the assessment of various organ damage parameters in their ability to provide additional predictive power of cardiovascular complications. Therefore, testing and
validating the clinical use of retinal vascular imaging for cardiovascular risk prediction and risk stratification, particularly in asymptomatic people, are warranted to further clarify.

What Are Technological Challenges in Retinal Vascular Imaging?

Although standardized photographic protocols are available for the assessment of retinal vascular changes, there are still different technological challenges in retinal vascular imaging that may lead to misclassification or less precision of the measurement. First, refractive error and axial length may affect the magnification and apparent dimensions of retinal structures on fundus photography.114 Other ocular factors, including retinal pigmentation, pupil dilation, presence of cataract, and other ocular media opacities, may vary image brightness, focus, and contrast, which significantly affect the measurement of retinal vascular changes.115-117 Furthermore, photographic technique and camera type may also affect the image quality for retinal fundus photography. Such possible ocular factors and confounders should be controlled for (eg, factoring in magnification effect and iris color) in the further development of retinal vascular imaging technology.

Currently, retinal vascular changes are either manually or semiautomatically assessed in reading centers. Observer’s manual input is still required, which may introduce additional variability in measurements. Further technical refinement should be performed to minimize variability in measurements. Full automation in the measurement process and abnormalities detection is still underdeveloped and not yet ready for end user.

Conclusions

The retinal vasculature is a unique biological model to study both the manifestations and origins of hypertension. Advanced retinal vascular imaging technologies have been developed to allow a more objective and precise assessment of retinal vascular changes. Further development of retinal vascular analyses and standardized measurement protocols, evaluation of the clinical use of retinal vascular imaging in assessing cardiovascular risk prediction, and using retinal vascular imaging to test antihypertensive treatments will allow the translation of retinal vascular imaging as a tool to improve the diagnosis, prognosis, and management of hypertension in clinical practice.

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Disclosures

None.

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Grassi G, Schmieder RE. The renaissance of the retinal microvascu-


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ONLINE SUPPLEMENT

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Supplemental Reference Section


**Supplemental Tables**

**S1.** A classification of hypertensive retinopathy based on prognosis of different signs and its relationship with cardiovascular disease outcomes from recent population-based data.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Signs</th>
<th>Cardiovascular Disease Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Mild</td>
<td>Generalized arteriolar narrowing</td>
<td>Incident stroke$^1$, cardiovascular mortality$^2$, renal dysfunction$^3$, incident coronary heart disease$^4,5$</td>
</tr>
<tr>
<td></td>
<td>Focal arteriolar narrowing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arteriovenous nicking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arteriolar wall opacification (silver or copper wiring)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Microaneurysm</td>
<td>Incident stroke$^1,6-8$, incident congestive heart failure$^9$, cardiovascular mortality$^7$, transient ischemic attack and acute ischemic stroke$^{10}$, stroke mortality$^7$, incident lacunar stroke$^{11}$, prevalent coronary heart disease and stroke$^{12}$, renal dysfunction$^3$</td>
</tr>
<tr>
<td></td>
<td>Hemorrhage (blot, dot, or flame-shaped)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hard exudates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cotton-wool spot</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>Moderate retinopathy signs plus optic disc swelling</td>
<td>Death (only clinic-based data$^{13}$)</td>
</tr>
</tbody>
</table>

$^1$ Incident stroke
$^2$ Cardiovascular mortality
$^3$ Renal dysfunction
$^4$ Incident coronary heart disease
$^5$ Transient ischemic attack and acute ischemic stroke
$^6$ Incident congestive heart failure
$^7$ Stroke mortality
$^8$ Incident lacunar stroke
$^9$ Prevalent coronary heart disease and stroke
$^{10}$ Renal dysfunction

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<td>Generalized arteriolar narrowing</td>
<td>Incident stroke$^1$, cardiovascular mortality$^2$, renal dysfunction$^3$, incident coronary heart disease$^4,5$</td>
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<tr>
<td></td>
<td>Focal arteriolar narrowing</td>
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<tr>
<td></td>
<td>Arteriovenous nicking</td>
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<td></td>
<td>Arteriolar wall opacification (silver or copper wiring)</td>
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<tr>
<td>Moderate</td>
<td>Microaneurysm</td>
<td>Incident stroke$^1,6-8$, incident congestive heart failure$^9$, cardiovascular mortality$^7$, transient ischemic attack and acute ischemic stroke$^{10}$, stroke mortality$^7$, incident lacunar stroke$^{11}$, prevalent coronary heart disease and stroke$^{12}$, renal dysfunction$^3$</td>
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<tr>
<td></td>
<td>Hemorrhage (blot, dot, or flame-shaped)</td>
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<td>Hard exudates</td>
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<tr>
<td></td>
<td>Cotton-wool spot</td>
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<tr>
<td>Malignant</td>
<td>Moderate retinopathy signs plus optic disc swelling</td>
<td>Death (only clinic-based data$^{13}$)</td>
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</table>

$^1$ Incident stroke
$^2$ Cardiovascular mortality
$^3$ Renal dysfunction
$^4$ Incident coronary heart disease
$^5$ Transient ischemic attack and acute ischemic stroke
$^6$ Incident congestive heart failure
$^7$ Stroke mortality
$^8$ Incident lacunar stroke
$^9$ Prevalent coronary heart disease and stroke
$^{10}$ Renal dysfunction

---
General population-based studies of the association between retinal vascular caliber with blood pressure (concurrent, past, future), target end-organ damage and cardiovascular disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>Race/Ethnicity</th>
<th>Sample size in the analysis</th>
<th>Retinal vascular caliber changes*</th>
<th>Outcomes</th>
<th>Adjustment for classical cardiovascular risk factors in the associations with incident cardiovascular events</th>
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<tr>
<td>Atherosclerosis Risk in Communities Study (ARIC), USA</td>
<td>45-73</td>
<td>White, Black</td>
<td>9,300</td>
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<td>Beaver Dam Eye Study (BDES), USA 43-84</td>
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<td>Multi-Ethnic Study of Atherosclerosis (MESA), USA</td>
<td>45-84</td>
<td>White, Black, Hispanics and Chinese</td>
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<td>Sample Size</td>
<td>Abnormality</td>
<td>Risk Factors</td>
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<td>Rotterdam Study, Netherlands</td>
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<td>Study Programme</td>
<td>Age Range</td>
<td>Ethnicity</td>
<td>Sample Size</td>
<td>Arteriolar narrowing and Vascular Changes</td>
<td>Blood Pressure</td>
<td>Co-Morbidity</td>
<td>Reference</td>
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<td>Singapore Cohort Study of Risk Factors for Myopia, Singapore</td>
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<td>Chinese, Malay, Indian</td>
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</tbody>
</table>

* Arteriolar narrowing is assessed by either smaller retinal arteriolar caliber or arterio-venous ratio
Supplemental Figures

S1.A
S1.B
S1. Assessment of retinal vascular changes using computer-assisted programs. Arterioles are in red and venules are in blue. Panel A shows retinal arteriolar and venular calibers were summarized as central retinal arteriolar (CRAE) and the central retinal venular (CRVE) equivalent respectively from retinal fundus photograph using the Interactive Vessel Analysis software (IVAN, University of Wisconsin, US). Panel B shows the Singapore I Vessel Assessment (SIVA, National University of Singapore, Singapore) program for measurement of novel geometrical retinal vascular parameters. Panel C shows tortuosity measurement, Panel D shows retinal fractal dimension measurement and Panel E shows bifurcation measurement.
S2. A screenshot of retinal arteriolar structure analyses using scanning laser Doppler flowmetry with automatic full-filed perfusion imaging analyses program⁴¹.