Retinal Vascular Caliber Measurements: Clinical Significance, Current Knowledge and Future Perspectives

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Retinal vascular caliber measurement · Retinal image analysis · Cardiovascular diseases

Abstract
The retinal vasculature provides a unique window to assess vascular health noninvasively and directly in vivo. Advances in fundus photography and retinal image analysis techniques have enabled the objective and accurate assessment of quantitative retinal vascular caliber measurement. Over the last decade, large population-based studies have shown that retinal vascular calibers are associated with a wide range of subclinical (e.g. atherosclerosis, inflammation and endothelial dysfunction) and clinical cardiovascular diseases (hypertension, diabetes mellitus, stroke, kidney and heart diseases). However, while retinal image analysis provided exciting possibilities to study the pathogenesis of these diseases, its direct applicability in a clinical setting as a ‘test’ to predict cardiovascular diseases is yet to be established, particularly within the context of being used as a population screening tool. Nevertheless, with continual development of retinal imaging techniques and newer understanding of the clinical significance of these retinal changes, there remains scope for the development of retinal vascular caliber measurements as a biomarker for vascular disease risk assessment in targeted areas and patient subgroups (e.g. patients with diabetes, suspected hypertension and stroke).

Introduction
The development of the ophthalmoscope in the 19th century opened a window on the living human retina and the microcirculation in a natural and noninvasive way. The potential of changes seen in the retinal blood vessels and for these changes to serve as ‘markers’ of systemic disease was soon recognized by the Scottish physician Robert Marcus Gunn, who in 1898 presented a series of observations he made on the retinal vessels in patients with stroke [1, 2]. The signs he described were generalized arteriolar narrowing, arteriovenous nicking, cotton-wool spots, intraretinal hemorrhages and papilledema. In 1974, Keith et al. [3] made the first attempt to relate these retinal signs to the survival of patients with hypertension. The 3-year survival of persons with grade I (mild retinal vessel signs) was 70% compared to only 6% in those with grade IV (severe signs). These signs subsequently became known as the classification for hypertensive retinopathy.
Following this landmark observation, other additional classification schemes for hypertensive retinopathy were proposed and their relationship with a wide spectrum of cardiovascular diseases and mortality was described (table 1) [3–6].

Although these classifications provided a better understanding of hypertensive retinopathy, application of these systems to a clinical setting proved difficult for several reasons. The natural sequence of these grades was not clear; for example, in some cases grade III was observed to occur before grade II. Furthermore, papilledema (grade IV) can develop in patients with malignant hypertension without showing any signs of earlier grades [7]. Most of the pioneering work was done in clinic-based populations with hypertension in a period with limited possibilities for treatment [2]. The more severe abnormalities were shown to be relatively uncommon in the general populations that were examined a few decades later, perhaps due to better control of blood pressure [8, 9]. Finally, the detection of retinal vessel signs with ophthalmoscopy has been demonstrated to be subjective and less reliable [1, 10, 11]. In particular, generalized retinal arteriolar narrowing, which is one of the earliest signs, proved difficult to quantify in an objective way [1, 12].

### Retinal Imaging and Vascular Caliber Measurements

Modern digital imaging systems have revolutionized the assessment of retinal photographs. Instead of subjective clinical assessment with a limited view of the retinal vessels, retinal photography captures a larger segment of the retina and allows a more objective documentation of major retinal vessels and its branches [12].

These new methods were applied to larger general population cohorts and demonstrated excellent repro-

**Table 1. Summary of different classification systems of retinal vessel signs of atherosclerosis and hypertension**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Retinal vessel signs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keith et al. [3]</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Mild to moderate narrowing or sclerosis of the arterioles</td>
</tr>
<tr>
<td>II</td>
<td>Moderate to marked arteriolar sclerosis, arteriovenous nicking, generalized and/or focal arteriolar narrowing</td>
</tr>
<tr>
<td>III</td>
<td>Marked arteriolar narrowing and focal constriction, retinal edema, cotton wool spots, hemorrhage</td>
</tr>
<tr>
<td>IV</td>
<td>Grade III plus papilledema</td>
</tr>
<tr>
<td><strong>Wagner et al. [3]</strong></td>
<td></td>
</tr>
<tr>
<td>Neurogenic</td>
<td>Mild generalized arteriolar narrowing</td>
</tr>
<tr>
<td>Acute (angiospastic)</td>
<td>Moderate generalized arteriolar narrowing, focal constriction, retinal edema, cotton wool spots, hemorrhage</td>
</tr>
<tr>
<td>Chronic nonprogressive</td>
<td>Marked generalized arteriolar narrowing</td>
</tr>
<tr>
<td>Chronic progressive</td>
<td>Generalized and focal arteriolar narrowing and sclerosis</td>
</tr>
<tr>
<td>Malignant</td>
<td>Papilledema</td>
</tr>
<tr>
<td><strong>Scheie [4]</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Barely detectable arteriolar narrowing or light reflex changes</td>
</tr>
<tr>
<td>II</td>
<td>Obvious arteriolar narrowing with focal irregularities or increased light reflex changes</td>
</tr>
<tr>
<td>III</td>
<td>Grade II + hemorrhage and/or exudates or copper-wire arterioles</td>
</tr>
<tr>
<td>IV</td>
<td>Grade III + papilledema or silver-wire arterioles</td>
</tr>
<tr>
<td><strong>Leishman [5]</strong></td>
<td></td>
</tr>
<tr>
<td>Involutional sclerosis</td>
<td>Arterioles: straight and narrow, no arteriovenous nicking, general picture of an aging fundus</td>
</tr>
<tr>
<td>Involutional sclerosis with hypertension</td>
<td>Arteriolar segment towards disc dilated, distal arteriolar segment narrow</td>
</tr>
<tr>
<td>Involutional sclerosis with advanced hypertension</td>
<td>Major arterioles dilated, arteriovenous crossing changes</td>
</tr>
<tr>
<td>Early hypertension in youthful vessels</td>
<td>Generalized arteriolar narrowing</td>
</tr>
<tr>
<td>Fulminating hypertension</td>
<td>Arterioles: narrowing, papilledema and retinal edema, hemorrhage, arteriovenous nicking</td>
</tr>
<tr>
<td>Severe hypertension with relative sclerosis</td>
<td>Grades 1–4</td>
</tr>
<tr>
<td><strong>Wong and Mitchell [6]</strong></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Presence of generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, or a combination</td>
</tr>
<tr>
<td>Moderate</td>
<td>Presence of blot or flame-shaped hemorrhage, microaneurysm, soft exudates or a combination</td>
</tr>
<tr>
<td>Malignant</td>
<td>Signs of moderate retinopathy with optic disc swelling</td>
</tr>
</tbody>
</table>
ducibility for the detection of well-defined qualitative retinopathy signs (kappa values ranged from 0.80 to 0.99 for microaneurysms and retinal hemorrhages) and good reproducibility for more subtle retinal arteriolar lesions (0.40–0.79 for focal retinal arteriolar narrowing and arteriovenous nicking) [12]. Over the last few decades, both hospital-based and population-based studies have shown that these qualitative retinopathy signs, as documented from photographs, are related to the risk of cardiovascular diseases [2]. However, the development of quantitative assessment of the retinal microvasculature has been more difficult.

In this respect, since the 1970s semiojective methods based on retinal photography or slide projection systems had been developed. These methods relied on obtaining a ratio between arteriolar and venular widths as an index of generalized arteriolar narrowing. In 1974, Parr and Spears [13, 14] developed a technique for evaluation of generalized arteriolar narrowing. They measured all retinal arteriolar blood column diameters in an area between half a disc diameter and one disc diameter from the optic disk margin. This region was selected because its vessels are unequivocally arterioles instead of arteries [2, 12]. Furthermore, in this region there was less overlap between the vessels than near or on the optic disc making the measurements more reliable. The measured arteriolar calibers were converted into a one-sum value representing the caliber of the retinal artery, named the ‘central retinal artery equivalent’ [12–14]. Hubbard et al. [12] later extended Parr’s method to venules and summarized these as ‘central retinal vein equivalent’. Using this technique, they developed a semiautomated system to evaluate more reliably and accurately retinal vascular calibers from high-resolution digitized fundus photographs. Hubbard et al. [12] developed formulas to generate summarized measures of retinal arteriolar [central retinal arteriolar equivalent (CRAE)] and venular [central retinal venular equivalent (CRVE)] calibers, as well as their dimensionless quotient [arteriovenous ratio (AVR)]. Furthermore, Knudtson et al. [15] made further refinements based on the six largest arterioles and venules to compute these summarized retinal vascular measures. These retinal vascular indices have been used in several large-scale epidemiological studies, which demonstrated substantial reproducibility for these retinal vascular caliber measurements (intraclass correlation coefficient ranged from 0.80 to 0.99) [12], providing further evidence that retinal photography offers a more sensitive and precise means of assessing architectural changes in the retinal vascular network [16–18].

Determinants of Retinal Vascular Calibers

Age

One of the most consistent findings regarding retinal vascular calibers is their association with age.

Retinal vascular calibers have been examined among children of different age ranges. One study reported retinal arteriolar and venular calibers among 20 infants born at term with normal birth weight [19]. The retinal arteriolar caliber was on average 85.5 μm, and the mean venular caliber was 130.0 μm [19]. There were no differences in the arterial or venule calibers between male and female infants. Compared to previously published results from the Sydney Childhood Eye Cohort [20], retinal arteriolar and venular calibers nearly doubled by the time a child was 6 years old (mean retinal arteriolar caliber of 165.6 μm and venular caliber of 232.0 μm). Over the same period of time, the body weight of the infant would have increased by more than 5-fold. The available data from adult populations suggest that while the retinal venular caliber remains approximately the same from the age of 6 onwards, the retinal arteriolar caliber continues to grow from infancy to adulthood to a mean of 202.3 μm in those above 43 years old [20]. These data suggest that retinal arteriolar caliber increases at a different pace compared to retinal venular caliber. Finally, among middle-aged and elderly subjects data from all large population-based studies have shown a converse association between retinal vascular calibers and age, namely that older persons have both smaller retinal arteriolar and venular calibers. Nevertheless, despite the consistency of this association the absolute differences in calibers among persons above 80 years compared to those who are 55–60 years are only in the order of magnitude of 10–15 μm [12, 21, 22]. Overall, these data suggest that after an initial increase in retinal vascular calibers with increasing age, from middle age onwards there is a decrease in these calibers.

Hypertension

Of the different systemic diseases, the strongest relationship has been reported between retinal vascular calibers and hypertension [12, 22–25]. Retinal arteriolar narrowing has long been recognized as one of the earliest sign of hypertension secondary to chronic exposure to increased blood pressure and is inversely related to higher blood pressure levels. This finding was subsequently confirmed in multiple population-based studies [12, 22–25]. A recent meta-analysis of five cross-sectional studies (including 19,633 subjects) showed that arteriolar caliber
decreased by 3.07 μm [95% confidence interval (CI): 2.40–3.73 μm] for every 10-mm Hg increase in arterial blood pressure [26]. Furthermore, studies have demonstrated that retinal artery narrowing is not only related to chronic exposure to hypertension, but might precede the development of hypertension [26].

In addition to the impact of blood pressure on the retinal vessels, it has been hypothesized that the primary feature of essential hypertension is increased peripheral vascular resistance in small vessels throughout the body, and therefore noninvasively accessible in the retinal microvasculature. Data from several longitudinal cohort studies provided the first prospective clinical evidence showing that narrower arteriolar calibers as reflected by a smaller CRAE preceded the development of clinical hypertension, and was not purely a secondary response to established hypertension [27–31]. A recent meta-analysis based on four population-based studies including 6,247 participants with follow-up periods ranging from 3 to 7 years showed that a smaller arteriolar caliber was associated with an increased risk of incident hypertension [meta-analysis relative risk (RR): 1.91; 95% CI: 1.56–2.34] [26]. Finally, both Atherosclerosis Risks in Communities (ARIC) and Beaver Dam Eye Study showed an association between a smaller AVR and an increased risk of hypertension. However, they did not present the retinal arteriolar caliber separately [27, 28].

Diabetes Mellitus

It has been hypothesized that microvascular pathology may play an important role in the pathophysiology of diabetes mellitus [32, 33]. Prospective data from the ARIC Study and Beaver Dam Eye Study showed that nondiabetic individuals with smaller AVR had a 50–70% higher risk of incident diabetes, independent of other cardiovascular risk factors [17, 34]. The Beaver Dam Study showed that this association is noticeably stronger in individuals with hypertension at baseline (RR: 3.41; 95% CI: 1.66–6.98) [34]. However, these studies did not examine the arteriolar and venular calibers separately. The Rotterdam Eye Study proposed that this association may be due to retinal venular dilatation instead of arteriolar narrowing and demonstrated an association of wider retinal venular caliber with impaired fasting glucose [35]. Furthermore, the Multi-Ethnic Study of Atherosclerosis (MESA), the Australian Diabetes, Obesity and Lifestyle (AusDiab) and Blue Mountains Eye Study also found an association between wider retinal arteriolar calibers and diabetes [36, 37]. Data from Asian populations including Chinese, Malay and Indians also reported an association between wider retinal arteriolar caliber and diabetes status [38, 39]. While the underlying biological mechanisms for these observations remain to be elucidated, experimental studies have shown that the administration of intravenous dextrose can cause dilatation of retinal venules in normoglycemic patients [40]. Moreover, reduced vascular reactivity associated with endothelial dysfunction and inflammatory processes may also play integral roles in the development of wider retinal arteriolar and venular calibers in diabetes [41].

Obesity, Lipids and Physical Activity

Obesity may have a profound effect on the eye, but the retinal vascular manifestations of obesity are poorly understood [42]. Interestingly, several studies showed that variations in retinal vascular caliber may also be associated with obesity correlates. Larger venular caliber, but not arteriolar caliber, was related to measures of obesity (greater body mass index and waist-hip ratio) and dyslipidemia (higher levels of plasma triglyceride and LDL cholesterol and lower levels of HDL cholesterol) [22, 43]. These patterns have been observed in several population-based studies including MESA and ARIC [44, 45]. Furthermore, prospective data from the Blue Mountains Eye Study further indicated that a larger retinal venular caliber may even predict the incidence of obesity over a 5-year period, suggesting the existence of microvascular dysfunction in the pathogenesis of obesity [46]. Closely related to obesity is a lack of regular moderate-to-vigorous-intensity physical activity, which is a well-known modifiable risk factor for cardiovascular diseases. Data from the Singapore Prospective Study Program, ARIC Study and MESA have consistently shown a relationship between lower levels of physical activity and wider retinal venular caliber [47–49]. Inflammation, oxidative stress, hyperleptinemia and nitric oxide dysregulation have all been implicated as potential pathways in the link between larger retinal venules and obesity development.

Atherosclerosis, Inflammation and Endothelial Function

Several population-based studies have examined the association between retinal vascular calibers and atherosclerosis, the key underlying pathological process of cardiovascular diseases [22, 43, 45, 50–52]. However, the evidence of a link between retinal vascular caliber and direct measures of atherosclerosis has not been consistently demonstrated. In the ARIC Study, smaller AVR was associated with carotid artery plaque but not intima-media thickness [50]. In addition, the Rotterdam
Study found an association between smaller AVR and carotid artery intima-media thickness [22]. Moreover, smaller AVR has also been independently associated with increased carotid artery stiffness, an early marker of atherosclerosis [22]. As the AVR is a composite measure and does not reveal which component (CRAE or CRVE) is related, it has been suggested that these retinal summary measures should be examined separately. Data from the Rotterdam Study revealed that these associations were largely explained due to larger retinal venular calibers [22]. Data from the Hoorn Study showed that retinal venular dilatation was associated with an increased intima-media thickness, although nonsignificantly after multivariable adjustment for cardiovascular risk factors, especially fasting insulin levels [51]. These findings, nevertheless, are contradictory to data from the Cardiovascular Health Study, which revealed no consistent independent association between smaller AVR and measures of large artery atherosclerosis [53]. Other markers of atherosclerosis which have been examined in relationship to retinal vascular caliber include coronary artery calcifications, left ventricular hypertrophy and peripheral artery disease as measured by the ankle-arm index. In the MESA, retinal arteriolar narrowing was related to left ventricular concentric remodeling and myocardial blood flow [54, 55]; in contrast, variations in retinal vascular caliber were not associated with coronary artery calcifications [56]. Furthermore, a larger venular caliber has been associated with a lower ankle-arm index [22].

Other markers of subclinical cardiovascular diseases include both inflammation and endothelial dysfunction, both considered key factors in pathogenic pathways. Data from several population-based studies showed an association between larger retinal venular caliber and various inflammatory markers, including C-reactive protein and leukocyte count [22, 57, 58]. In the Beaver Dam Eye Study, indicators of endothelial dysfunction, such as soluble intercellular adhesion molecule-1 and serum E-selectin, were also shown to be associated with a larger retinal venular caliber [58]. More recently, endothelial dysfunction has been assessed with brachial flow-mediated dilatation examination or dynamic vessel analysis of the retinal vessel [59, 60]. These examinations showed reduced responses in patients with larger venular calibers. These observations corroborate findings from experimental studies, which demonstrated an increase in the diameter of retinal venules, but not arterioles, after administration of lipid hydroperoxide into the vitreous of rats with a resultant increase in the number of leukocytes in the retinal microvasculature [61]. Dilatation of retinal venules has been postulated to be a result of increased production of nitric oxide secondary to release of inflammatory mediators [60]. These data suggest that both inflammation and endothelial dysfunction may play an important role in linking retinal venular dilatation with systemic diseases.

Genetics

The Beaver Dam Eye Study reported that retinal vascular calibers were more highly correlated between relatives than between unrelated individuals, an observation proposed to be due to shared genes [62]. This is in keeping with data from a recent twin study, showing that 70% of the variance in retinal arteriolar caliber and 83% of the variance in retinal venular caliber were attributable to genetic factors [63]. Newer data from the Beaver Dam Eye Study, based on genome-wide linkage scan, further reinforce the genetic contribution to the variation in retinal vascular calibers, independent of hypertension and other confounders [64]. The investigators showed that the linkage regions for retinal vascular calibers overlap with regions that have been previously associated with essential hypertension, coronary heart disease (CHD), endothelial dysfunction and vasculogenesis [64, 65]. Finally, a genome-wide association study was performed consisting of 15,358 unrelated Caucasian individuals from four population-based discovery cohorts and subsequently in the replication phase, 6,652 persons from four independent Caucasian cohorts [66]. This study demonstrated four novel loci (19q13, 6q24, 12q24 and 5q14) associated with retinal venular caliber. Of these four loci, the locus on 12q24 was also associated with CHD and hypertension [66]. While the currently available data regarding the genetic basis of retinal vascular changes are limited, findings from recent studies clearly demonstrate the usefulness of retinal image analysis in advancing our understanding of the pathogenesis of cardiovascular disease.

Birth Weight

Children with low birth weight are at an increased risk of developing cardiovascular diseases during their adult life. In this association, damage to the small blood vessels may play an important role [67]. Over the last few years, several studies have used retinal imaging to assess the microcirculation in children with a low birth weight. In a sample of 1,369 young children, Mitchell et al. [68] found that the mean retinal arteriolar caliber was narrowed by 2 µm per 1 kg reduction in birth weight. Data from the Twin Eye Study in Tasmania also showed that children who were born small had smaller mean retinal arterioles [69]. In contrast, previous data from the Singa-
pore Cohort Study of the Risk Factors for Myopia and the Avon Longitudinal Study indicated that neither low birth weight nor preterm birth was associated with narrowed retinal arterioles [70, 71]. However, the effect of ocular magnification and small sample sizes may have limited the ability to detect these associations. Overall, an increasing body of evidence suggests that low birth weight, as a surrogate for disadvantaged intrauterine environment including restriction in nutrition and growth, results in adaptive microcirculatory structural changes, which are likely to be maladaptive to the environment after birth and later in life.

Retinal Vascular Caliber and Brain Diseases

Stroke

As the retinal microvasculature shares many features with the cerebral circulation including embryological origin, anatomical and physiological characteristics (such as blood-tissue barrier), it has been suggested that the retinal vascular caliber may in particular provide insights into vascular pathology in the brain [72]. In the ARIC Study, smaller retinal AVR was reported to be associated with an increased risk of stroke, especially cerebral infarction [73]. This association was confirmed in the Cardiovascular Health Study [74]. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), among persons with diabetes, a smaller retinal arteriolar caliber was associated with a 50% higher risk of stroke mortality [75]. Larger retinal venular caliber was also associated with a 1.7 times higher risk of stroke mortality [75]. The association of stroke with wider retinal venular caliber was further confirmed in the Rotterdam Study where a larger venular caliber was also associated with a 12% higher risk of stroke and a 15% higher risk of cerebral infarction, while retinal arteriolar narrowing was neither related to the risk of stroke nor to the risk of cerebral infarction [76]. McGeechan et al. [77] performed a meta-analysis including data from 20,798 participants and showed that retinal venular caliber, but not retinal arteriolar caliber, was related to an increased risk of stroke (RR per 20-μm increase in venular caliber: 1.15; 95% CI: 1.05–1.25). Inclusion of retinal venular caliber in prediction models containing traditional stroke risk factors re-assigned 10.1% of people at intermediate risk into different, mostly lower, risk categories [77]. With respect to stroke subtypes, the above-mentioned studies have mainly focused on cerebral infarction, which comprises up to 80% of all strokes. With respect to the second most common subtype, intracerebral hemorrhage, one study showed that a larger retinal venular caliber was also related to this subtype (RR per SD increase in venular caliber: 1.53; 95% CI: 1.09–2.15) [78].

Cerebral Small Vessel Disease

In ARIC, Cardiovascular Health Study (CHS) and the Rotterdam Study, which examined community-based cohorts of middle-aged and elderly predominantly healthy people, retinal vascular changes including retinopathy signs and retinal vascular calibers were associated not only with incident stroke [73–77], but also with subclinical MRI-defined changes, including cerebral infarction, white matter lesions and atrophy [74, 79–83]. Furthermore, data from the Rotterdam Scan Study showed that persons with larger retinal venular caliber were at 70% higher risk of progression in periventricular or subcortical white matter lesions and 59% increased risk of incident lacunar infarcts [84]. Subsequently, the association between retinal vascular calibers and lacunar infarcts has been confirmed in other population-based and clinic-based studies [85, 86].

Cognitive Decline and Dementia

Finally, with respect to cognitive decline and dementia, several large population-based studies have shown that retinal vascular changes are associated with cognitive impairment [87–92]. Furthermore, in the ARIC Study, in patients without stroke, retinal vascular changes were associated with poorer cognitive function [93]. In the Rotterdam Study, it was observed that larger retinal venular caliber was associated with an increased risk of dementia and in particular vascular dementia, which was in line with observations in stroke and cerebral small vessel disease [94]. However, these data did not support a role for vascular pathology underlying retinal venular widening in the etiology of Alzheimer’s disease. The link between retinal microvascular abnormalities and Alzheimer’s disease remains inconclusive [94].

Overall, these data suggest that the retinal microvasculature provides an ideal opportunity to explore the possibilities of elucidating the pathophysiology of age-related brain diseases including stroke and dementia.

Retinal Vascular Caliber and CHD

Studies suggest that retinal vascular caliber predicts CHD more strongly in women than men, possibly reflecting the greater contribution of microvascular disease
to CHD development in women [95]. In the ARIC Study, smaller AVR was associated with an increased risk of incident CHD and acute myocardial infarction in women but not men [96]. In the CHS, larger retinal venular caliber was associated with a 3-fold increased risk of incident CHD independent of cardiovascular risk factors [97]. A smaller retinal arteriolar caliber was also associated with a 2-fold risk of incident CHD, comparing largest with smallest arteriolar caliber quartiles. Women with larger retinal venular or narrower arteriolar calibers each had a 30% higher risk of CHD even after adjusting for other known cardiovascular risk factors [97]. In the Blue Mountains Eye Study, middle-aged persons of 49–75 years with larger venular caliber had a 2-fold increased risk of CHD mortality after adjusting for traditional risk factors. Additionally, in women, a smaller arteriolar caliber was associated with a 1.5 times higher risk of CHD mortality [98]. In combined analysis of the Blue Mountains Eye Study and the Beaver Dam Eye Study, smaller arterioles and larger venules were associated with a 20–30% increased risk of CHD mortality independent of cardiovascular risk factors [99]. In another meta-analysis including 22,159 participants, McGeechan et al. [100] found that retinal vessel caliber changes of both wider venules and narrower arterioles were associated with an increased risk for CHD in women, but not in men. Finally, studies have shown that in the general population, a smaller retinal arteriolar caliber was associated with left ventricular concentric remodeling, determined from cardiac MRI, even after adjusting for traditional risk factors [53, 54]. These findings suggest that retinal vascular caliber may even provide insights into early subclinical myocardial abnormalities.

**Retinal Vascular Caliber and Kidney Diseases**

Experimental studies have shown a link between pathological changes in the retinal and renal vasculature [101]. However, there have been few studies that have explored the independent association of retinal vascular abnormalities with kidney disease. So far, studies have largely focused on qualitative retinopathy signs in relation to markers of renal dysfunction [102, 103]. These findings raise the possibility that retinopathy and nephropathy may share common pathogenic pathways (e.g., endothelial dysfunction or inflammation), even in nondiabetic individuals, and highlight the need to monitor renal function in individuals with retinopathy. More recently, data from the MESA Study showed that a smaller arteriolar caliber in whites was associated with a higher risk of developing chronic kidney disease (RR lowest vs. highest tertiles: 1.78; 95% CI: 1.01 [104, 105]. Two other studies among Asian participants, including Malays, Indians and Chinese, confirmed a link between a smaller arteriolar caliber and chronic kidney disease [105, 106]. Finally, studies among patients with diabetes mellitus type 1 showed that changes in retinal vascular calibers were related to both incidence of gross proteinuria and morphological parameters obtained from renal biopsy specimens [107, 108]. However, further studies are required to confirm these associations and further elucidate the exact link between changes in retinal vascular calibers and kidney disease [109].

**Retinal Vascular Caliber and Ocular Diseases**

Apart from the associations with systemic and cardiovascular diseases, studies have also examined the direct link between retinal vascular calibers and a range of ocular diseases.

**Diabetic Retinopathy**

Prospective studies, including the WESDR Study, suggest that in people with type 1 diabetes, larger retinal venular caliber is associated with progression of mild to more severe levels of diabetic retinopathy, including proliferative retinopathy [110, 111]. In contrast, studies on type 2 diabetes are scarce and the findings are inconclusive based on the limited evidence [112]. Future research is still needed to assess the ability of retinal vascular caliber measures to provide clinically useful prognostic information that might add to risk prediction of diabetic retinopathy over and above the contribution from traditional risk factors, including glycemic levels and the duration of diabetes [113].

**Age-Related Macular Degeneration**

Thus far, several studies have also examined the association between retinal vascular caliber and age-related macular degeneration (AMD) [114–116]. The results from these studies have been inconsistent. Data from the Singapore Malay Eye Study revealed that wider venular caliber was independently associated with early AMD, whereas no relationship was found between retinal arteriolar caliber and AMD [114]. The Handan Eye Study showed that wider retinal arteriolar caliber was related to early AMD and venular caliber was not related to AMD [115]. In contrast to both these studies, cross-sectional data from the Beaver Dam Eye Study showed no associa-
tion between retinal vascular calibers and AMD [116]. Furthermore, prospective data from the Beaver Dam Eye Study and the Rotterdam Study could not confirm an association between retinal vascular calibers and incident AMD [116, 117].

Primary Open-Angle Glaucoma

Few studies, thus far, looked at the relationship between retinal vascular caliber and primary open-angle glaucoma (POAG). Patients with POAG have been reported to have significantly smaller arteriolar calibers than age-matched control persons [118–120]. Furthermore, it has been suggested that retinal vascular caliber changes are associated with a decreased retinal nerve fiber layer thickness as measured with optical coherence tomography [121]. Due to the cross-sectional nature of these studies it was not possible to establish whether the described changes in retinal vascular caliber were a cause or consequence of neuronal loss. In contrast, in other studies no differences for either arteriolar or venular calibers were observed in OAG patients compared to control persons [122]. Prospective data from the Rotterdam Study did not show an association between retinal vascular caliber and incident POAG [123]. Further prospective studies are needed to unravel the exact role of retinal vasculature in the development of POAG.

Retinal Vein Occlusion

Finally, one study from Korea examined the association between retinal vascular caliber and retinal vein occlusion among 10,890 participants who underwent a health checkup [124]. Persons who had a retinal vein occlusion had both narrower retinal arteriolar and venular calibers compared to age- and gender-matched controls. Future studies are needed to confirm these findings in patients with retinal vein occlusion.

Limitations of Retinal Vascular Caliber Measurements

While retinal image analysis provided exciting possibilities, its applicability in the clinical setting is yet to be established, partly due to a number of methodological limitations. First, the formulas utilized to combine individual retinal vascular calibers into summarized indices are based on empirical models. The Parr-Hubbard formulas for the summary measures CRAE and CRVE were derived from examination of a large number of retinal images using a root mean square deviation model that best fit the observed data [12–14]. More recently, Knudtson et al. [15] developed modified formulas for summarizing retinal vascular caliber, and demonstrated clear superiority of their formula over the previously used Parr-Hubbard formulas. As these are summary measures, further refinements are required to reflect true values of the retinal vascular calibers.

Second, existing retinal vascular research has largely focused on differences in retinal vascular calibers between groups of people. To allow the use of retinal vascular measurement as a potential risk stratification tool in a clinical setting, however, retinal image analysis must produce results that enable an assessment of absolute risk in individual patients. The measurement of absolute retinal vascular caliber, for example, is critical to this development. This requires addressing the issue of a magnification effect from retinal photography, either by incorporating an adjusted measurement to compensate for this effect or using dimensionless measurements [22]. While there are already a few methods to adjust for magnification using ocular biometric data, its applicability on digitized retinal photographs is unknown.

Third, current population-based studies have used retinal caliber measurements obtained from one retinal image. However, it has been shown that retinal caliber may vary up to 15% depending on the moment in the cardiac cycle, when the image was taken [125]. Further standardization is required to improve the accuracy of these measurements.

Fourth, despite the vast amount of data on retinal vascular measurement in numerous population-based studies, there is a lack of knowledge about the normative data for this measurement. Defining what is normal and abnormal is crucial for a clinical tool development. One of the challenges in deriving normative data using studies in the adult populations has been the difficulty to completely control for the confounding effect of systemic (e.g., hypertension, diabetes, smoking, or medication) processes on retinal vascular caliber measurements. Studying retinal vascular caliber in healthy children and young adults, who are generally free of these influences, may provide better understanding of the reference data for this important vascular variable.

Finally, the retinal vascular caliber measurements do not reflect the 3-dimensional architecture or the functional changes of the retinal microvasculature. Therefore, the full potential of retinal image analysis in relationship to the prediction of cardiovascular diseases remains undetermined.
Future Directions of Retinal Vascular Imaging

There are presently efforts underway to examine novel retinal vascular parameters in relation to cardiovascular diseases. These include both local and global vascular topographic features, including the branching angles of blood vessels, retinal vessel tortuosity and fractal dimension [126]. These new retinal vascular parameters indicate how optimally designed and developed the retinal microvascular system is, and therefore may also reflect the state of the systemic and brain microcirculation. Variations from the optimal geometry are known to occur in certain conditions, such as diabetes mellitus. Similar variations may occur in other cardiovascular diseases and need to be explored further. Finally, novel technologies, such as the laser Doppler flowmeter or dynamic vessel analysis of retinal vascular diameter in response to flickering light, are making it possible to examine dynamic and functional aspects of the retinal microvasculature [127]. These dynamic and functional parameters will complement the static measurements in identifying novel retinal vascular abnormalities that may serve as early biomarkers for the prediction of cardiovascular diseases.

Conclusions

The retina provides an ideal opportunity to explore the possibilities of elucidating novel noninvasive biomarkers for cardiovascular diseases. Over the last decade, advances in retinal imaging techniques have allowed the development of accurate and reliable quantitative parameters such as retinal vascular calibers. Using these parameters several large population-based studies have shown that retinal vascular calibers may provide additional information on the risk of cardiovascular diseases beyond traditional cardiovascular risk factors. However, the full potential of retinal image analysis techniques remains undetermined. With the continuous development and advancement of retinal imaging techniques, there still remains scope for improvement in the quantification of retinal microvascular parameters, which may be utilized as noninvasive biomarkers for cardiovascular diseases.

References

3. Keith NM, Wagener HP, Barker NW: Some conditions, such as diabetes mellitus. Similar variations may occur in other cardiovascular diseases and need to be explored further. Finally, novel technologies, such as the laser Doppler flowmeter or dynamic vessel analysis of retinal vascular diameter in response to flickering light, are making it possible to examine dynamic and functional aspects of the retinal microvasculature [127]. These dynamic and functional parameters will complement the static measurements in identifying novel retinal vascular abnormalities that may serve as early biomarkers for the prediction of cardiovascular diseases.

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