Retinal microvascularisation abnormalities and cardiovascular risk

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Summary The progress of retinal imaging techniques has made retinal microvascular circulation easier to study. A number of observational studies were conducted to characterise the different abnormalities encountered and to determine the factors contributing to their onset. Three lesion groups were highlighted, including reduced arteriolar diameter, venular dilatation and retinopathy lesions. Retinal arteriolar narrowing signals the presence of hypertension (current or old) and the risk of hypertension onset. A genetic factor was implicated in this relationship. Venular dilatation and retinopathy correlate with the presence of diabetes, obesity and metabolic disorders. This association appears to be mediated partly by the presence of endothelial dysfunction and inflammation. The relationship between these abnormalities and cardiovascular risk was also studied in a number of longitudinal studies: the presence of retinal microvascular abnormalities is related with an increased risk of cardiovascular morbidity and mortality predominantly in individuals under the age of 75. More specifically, retinopathy is correlated with the presence of cerebral white matter lesions detected by MRI, an increased stroke risk and deterioration in cognitive function. On the cardiovascular level, a correlation was demonstrated between diminished coronary reserve, increased coronary calcifications observed by CT scan, coronary morbidity and mortality, and risk of heart failure. New techniques of retinal imaging, such as laser Doppler flowmetry, are still undergoing assessment and will help further to clarify these correlations.

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Résumé La microvascularisation rétinienne grâce au progrès des techniques d’imagerie rétinienne, peut être facilement étudiée. De nombreuses études observationnelles ont été réalisées afin de caractériser les différentes anomalies retrouvées et déterminer les facteurs favorisant leur apparition. Trois groupes de lésions sont mis en évidence : réduction du diamètre artériolaire, dilatation veineuse et lésions de rétinopathie. La diminution du diamètre artériolaire signe la présence d’HTA (actuelle ou ancienne) mais également le risque de survenue d’HTA. Il a été montré l’implication d’un facteur génétique dans cette relation. La dilatation veineuse et la rétinopathie sont, elles, corrélées à la présence de diabète, d’obésité, de syndrome métabolique. Cette association semble être médiee en partie par la présence de dysfonction endothéliale et d’inflammation. La relation entre ces anomalies et le risque cardiovasculaire a également été étudiée dans de nombreuses études longitudinales : la présence d’anomalies de la microvascularisation rétinienne est corrélée, de façon prédominante chez les personnes de moins de 75 ans, à une augmentation du risque de morbidité cardiovasculaire. De manière plus spécifique, au niveau cérébral, la rétinopathie est corrélée avec : la présence d’anomalies de la substance blanche à l’IRM, une augmentation du risque d’AVC et de détérioration des fonctions cognitives. Au niveau cardiovasculaire, il a été montré une corrélation avec une diminution de la réserve coronaire, une augmentation des calcifications coronaires au scanner, de morbidité coronarienne et d’insuffisance cardiaque. De nouvelles techniques comme la fluxmétrie à laser Doppler sont en cours d’évaluation et permettront peut-être de mieux préciser ces corrélations.

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Abbreviations

AVR arteriole to venule ratio
VD venular dilatation
AVnicking arteriovenous nicking
FAN focal arteriolar narrowing
GAN generalised arteriolar narrowing
CHD coronary heart disease
L VH left ventricular hypertrophy
CHF cardiac heart failure

Retinal microvascularisation, easily accessible with non-invasive procedures, appears to share the same physiological and anatomical characteristics as cerebral and coronary microvascularisation [1]. Retinal microvascularisation abnormalities could therefore reflect those observed in cerebral and coronary microvascularisation. Progress in computerised retinal photographic techniques [2–4] has enabled more accurate and reproducible analyses of retinal microvascularisation. A number of studies involving large population samples have therefore been conducted to try and understand which factors contribute to developing retinal microangiopathy, and its link with the onset of a cardiovascular event.

Background

By the end of the 19th century, Marcus Gun had described the correlation between retinal microvascular signs and hypertension, nephropathies and cerebrovascular diseases [5–7]. In 1939, Keith, Wagener, and Baker established the prognosis value of hypertensive retinopathy, specifically three-year survival at grade I (mild to moderate retinal arteriolar narrowing) was estimated to be 70% while that at grade IV (papillary oedema) was 6% [8]. As the arterioles could not be visualised in peripheral organs, the authors concluded that the retina offered a singular opportunity to study microcirculation in clinical practice.

The clinical interest in retinopathy, however, has remained limited. The correlation between these abnormalities and the cardiovascular disease was never clearly demonstrated in all the studies due to a number of biases, including the presence of confounding factors like hypertension, the lack of a control group, the lack of clinical outcomes, a studied population with severe uncontrolled hypertension that was not representative of the general population, and an ophthalmoscopic examination technique subjective and non-reproducible.

New techniques have allowed for the quantification of retinal vascularisation characteristics in a more objective and reproducible way. Thus, new data has emerged in an attempt to characterise the prevalence and incidence of these changes in retinal microcirculation, their relationship with cerebral and coronary microangiopathy and macroangiopathy, and therefore the role of retinal microcirculation as a risk marker of cardiovascular morbidity and mortality (since the cause and effect relationships have yet to be established).

Different retinal microcirculation signs and their relationship with cardiovascular risk factors

Most current studies use high-resolution retinal photographs analysed according to standardised protocols and using computer assisted method [9,10,2].
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Retinopathy

Retinopathy screening (considered present if one of these lesions exist: microaneurysm, haemorrhage, cotton wool spots, hard exudate, venular beading, neovessel formation) has a reproducibility of 0.80 to 0.99 (Fig. 1). These abnormalities are common during diabetes, but the earliest stages of some (retinal haemorrhages, microaneurysms and cotton wool spots) can be observed outside of diabetes. More recent studies have shown the prevalence of these lesions in 9% to 10% of the general population over the age of 42.

The three main factors behind its onset and development in diabetic patients are the duration of diabetes, the quality of glycemic and blood pressure control. The epidemiologic study of a diabetic cohort (the Wisconsin Epidemiologic Study of Diabetic Retinopathy WESDR) reported a retinopathy prevalence of 25% in patients with type 1 diabetes for five years and 80% in patients with type 1 diabetes for more than 15 years [11]. The importance of the hyperglycemia was demonstrated in epidemiologic studies and in the DDCT [12] and UKPDS studies [13]. The UKPDS study also demonstrated that strict blood pressure control reduced the likely development of retinopathy independently of hyperglycemia [13]. New data suggest that lipid-lowering therapy could also decrease the use of laser treatment [14].

Figure 1. Retinopathy associating microaneurysms, retinal haemorrhages and cotton-wool spots.

Figure 2. Arterio-venous nicking — the rigid arteriole compresses the vein as they cross within a common adventitial sheath.

Figure 3. Focal arteriolar narrowing.

Figure 4. Semi-automatic measurement of the arteriole to venule ratio according to the Hubbard method.
Apart from diabetes, hypertension is also a significant risk factor in the onset of these retinal abnormalities. They are more often associated with AVnicking, and arteriolar abnormalities (retinal arteriolar narrowing and copper appearance of the arteriolar wall). The different prospective cohort studies also demonstrated a correlation between retinopathy and body mass index, age, African-American origin [15—17], and more controversially, an increase in fibrinogen and triglycerides [15,17]. In the Cardiovascular Health study, retinopathy was associated with the presence of infraclinical atherosclerosis markers like carotid plaque and increased intimal medial thickness of the carotid artery [18].

The significance of its presence in normotensive patients without diabetes is still poorly defined. Its prevalence here is 2.6% to 8.6% [19]. Its role in predicting the onset of diabetes is controversial. Indeed, while it is associated with an increased risk in diabetes onset in young people and those with a family history of diabetes [20] in 2 epidemiologic studies, other prospective studies (Blue Mountains Study [21] and Beaver Dam [22]) have not confirmed this association [23].

The relationship between retinopathy and obesity is not clear. However, it appears that obesity increases the risk of developing retinopathy in patients with type 1 [12] and type 2 [13] diabetes.

**Arteriolar and venular abnormalities**

Focal arteriolar abnormalities include a FAN and the AVnicking (Figs. 2 and 3). These signs are less reproducible (0.4 to 0.7) [24,25]. They correlate with age and hypertension [10].

The measurement of the retinal vascular caliber has long been assessed using a ratio (arteriolar diameter over venular diameter, AVR). Since the diameter of veinules was then considered stable, a decreased ratio was therefore considered equivalent to arteriolar narrowing. The emergence of a semi-computerised method using software (Fig. 4) enabled the obtaining of more accurate and reproducible measurements of arteriolar and venular diameters (inter- and intra-technician reproducibility reaching 0.78 to 0.99) [3,26,27]. It was then demonstrated that a decreased AVR could also be secondary to an increased venular diameter [28,29]. The change in arteriolar and venular diameter reflects different physiopathological processes (Tables 1 and 2).

Arteriolar narrowing is considered as a sign of hypertension, of a history of hypertension in the last three to six years [10] or even as a risk factor for the onset of hypertension in normotensive individuals [30—33]. Four prospective studies with large population samples, namely the Atherosclerosis Risk In Communities (ARIC) study [30], Beaver Dam Study [31], Blue Mountains Eyes Study [32] and Rotterdam Study [33] (the first two using the AVR and the other two using the arteriolar diameter) demonstrated that the presence of a decreased arteriolar diameter is a risk factor, regardless of other factors, for developing hypertension within three to 10 years in normotensive individuals. These observations therefore strengthen the hypothesis that increased peripheral resistance, reflected by the narrowing of the arteriolar diameter, could be one of the factors contributing to the onset of hypertension [33]. Similarly, the Beaver Dam Study confirmed this hypothesis by demonstrating that there was a genetic contribution in determining retinal vessel diameters and multiple genome regions related to the blood pressure regulation system, endothelial function and angiogenesis are involved [34].

Concerning the increased retinal venular diameter, it has not been proven to be linked with hypertension. Still, it does correlate with the presence of diabetes, obesity, metabolic disorders, smoking, diagnostic inflammatory
### Table 2  Results of different longitudinal studies.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Size of study (n=)</th>
<th>Retinal lesions</th>
<th>Outcome</th>
<th>Result</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac</strong>&lt;br&gt;MESA [46]&lt;br&gt;ARIC [17]</td>
<td>4593&lt;br&gt;11612</td>
<td>GAN&lt;br&gt;Retinopathy</td>
<td>Concentric LVH Hospitalisation or death due to cardiac insufficiency</td>
<td>Yes&lt;br&gt;Yes, even in the sub-group without hypertension or diabetes or heart disease</td>
<td>492 in 7 years</td>
</tr>
<tr>
<td><strong>Coronary heart disease</strong>&lt;br&gt;MESA [51]</td>
<td>6147</td>
<td>Retinopathy</td>
<td>Increased coronary calcium score</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>CVHS [56]&lt;br&gt;BMES [53]</td>
<td>1992&lt;br&gt;3654</td>
<td>GAN, VD&lt;br&gt;AVR, GAN</td>
<td>Decreased coronary reserve Incidence of CHD Mortality secondary to CHD</td>
<td>Yes&lt;br&gt;Yes</td>
<td>115 in 5 years&lt;br&gt;192 in 9 years</td>
</tr>
<tr>
<td>BMES + BDES [54]</td>
<td>7494</td>
<td>GAN, VD</td>
<td>Mortality due to CHD</td>
<td>Only in the youngest sub-group of 49–75 years</td>
<td>653 in 10.9 years</td>
</tr>
<tr>
<td><strong>Cerebral</strong>&lt;br&gt;ARIC [50]</td>
<td>1684</td>
<td>Retinopathy, FAN, AV nicking</td>
<td>Cerebral infarction observed by MRI</td>
<td>Yes</td>
<td>183</td>
</tr>
<tr>
<td>CVHS [18]</td>
<td>1717</td>
<td>AVR, AV nicking</td>
<td>Cerebral infarction observed by MRI, white matter lesions</td>
<td>Yes</td>
<td>496</td>
</tr>
<tr>
<td>ARIC [16]</td>
<td>1684</td>
<td>Retinopathy</td>
<td>White matter lesions observed by MRI Stroke</td>
<td>Yes</td>
<td>186</td>
</tr>
<tr>
<td><strong>Cerebral</strong>&lt;br&gt;CVHS [56]</td>
<td>1992</td>
<td>GAN</td>
<td>Stroke</td>
<td>Yes</td>
<td>113 in 5 years</td>
</tr>
<tr>
<td>ROTT [49]</td>
<td>5540</td>
<td>GAN</td>
<td>Stroke</td>
<td>No</td>
<td>411 in 8.5 years</td>
</tr>
<tr>
<td>ARIC [48]</td>
<td>10358</td>
<td>Retinopathy AVR</td>
<td>Stroke</td>
<td>Yes&lt;br&gt;No</td>
<td>110 in 3.5 years&lt;br&gt;No</td>
</tr>
<tr>
<td>BMES [15]</td>
<td>3654</td>
<td>Retinopathy</td>
<td>Cerebrovascular events</td>
<td>Only in the sub-group without diabetes</td>
<td>132 in 7 years</td>
</tr>
<tr>
<td>BMES + BDES [54]</td>
<td>7494</td>
<td>GAN, FAN, AV nicking</td>
<td>Cerebrovascular events Cerebrovascular mortality</td>
<td>No</td>
<td>299 in 10.9 years</td>
</tr>
</tbody>
</table>

AVR: arteriole to venule ratio; VD: venous dilatation; AV nicking: arteriovenous nicking; FAN: focal arteriolar narrowing; GAN: generalised arteriolar narrowing; CHD: coronary heart disease.
markers, endothelial dysfunction and atherosclerosis markers (carotid plaque, intimal medial thickness and aortic calcification) [10,35,36]. Venular dilatation appears to be caused by the presence of retinal hypoxia [37].

In the population-based Blues Mountains Eye Study, the presence of retinalVD was associated with obesity and the onset of obesity at five years or a significant weight gain [38]. This association may be explained in several ways. The presence of a chronic inflammatory syndrome and endothelial dysfunction was described in obese individuals, particularly when there was also a metabolic disorder and insulin resistance [39,40]. In addition, the same correlation was further established between wider retinal venules [35,41] and the presence of a chronic inflammatory syndrome and endothelial dysfunction. Moreover, increased blood volume and leptin levels were noted in obese individuals, which could modify retinal vessel calibre via nitric oxide [42].

Hypertension and diabetes are correlated with the onset of certain vascular ophthalmologic diseases, like central retinal vein occlusion, arteriolar embolisms, retinal artery occlusion and non-arteritic optic neuritis. Central retinal vein occlusion and retinal arteriolar embolism are associated with increased cardiovascular mortality [43,44].

**Relationship with cardiovascular morbi-mortality and cardiac and cerebral micro- and macrovascular abnormalities**

Retinal microcirculation shares the same anatomical properties that the microvascularisation presents in other organs like the brain.

Several studies have demonstrated a relationship between retinopathy and the risk of nephropathy and amputation in diabetic patients regardless of other risk factors [45].

The relationship between retinal and coronary microcirculation is more difficult to prove. The study of an American population cohort between the ages of 49 and 73 by the ARIC [17] showed that retinopathy (and not changes in arteriolar and venular diameters) doubled the risk of developing an episode of heart failure regardless of other factors. The risk trebled in the sub-group with no history of coronary artery disease. This association therefore prompts the idea that microcirculation lesions could play a role in the onset of heart failure. In addition, a prospective study on a population between the ages of 45 and 84 with no medical history (Cardiovascular Multi-Ethnic Study of Atherosclerosis, MESA [46]) showed that a generalised decrease in the arteriolar diameter was associated with LV concentric remodelling regardless of other factors. This association was also witnessed in the normotensive sub-group. It was not, however, significant after adjustment with the presence of retinopathy. Retinal venule dilatation only correlated with ventricular remodelling in women. The physiopathological mechanism of this association remains a little unclear. The relationship between retinal and cardiac microcirculation abnormalities requires further studies.

Significant anatomical, embryological and physiological similarities between the cerebral and retinal microcirculation were demonstrated [1]. Therefore, examining retinal abnormalities enables a better understanding of the physiopathology of the cerebral microvascular changes. One of the prospective studies concerning an American population with no history of stroke, namely the ARIC study [16], showed an 11% prevalence of cerebral white matter lesions observed by MRI. These lesions were associated independently with an increased risk of stroke [48] (CI = [1.5–7.7]). Similarly, the presence of retinopathy, FAN, and AV nicking was associated with an increased risk of stroke (RR of 4) regardless of other factors. The presence of both retinopathy and cerebral white matter lesions is then associated with a stroke relative risk at 5 years of 18.1 (CI = [9–55.4]). The physiopathology of these white matter lesions is not well known. However, it appears they are markers of cerebral microangiopathy and a breakdown of the blood-brain barrier. Moreover, the retinal lesions, which have a stronger correlation with stroke risk and the presence of cerebral white matter lesions, are retinopathy lesions [47]. Thus, we can assume that retinal microcirculation abnormalities reflect cerebral microcirculation abnormalities and therefore the risk of a cerebrovascular disease. Similarly, several prospective studies involving large samples of the general population [15,18,48–50] showed that retinopathy correlated with an increased stroke risk cerebral infarction observed by MRI, cerebral atrophy and a deterioration of cognitive function. This correlation was weaker for the older populations (> 75 years). The correlation between GAN and the risk of stroke was not confirmed in all studies [15,48,49,54,56].

The relationship between retinal microvascularisation abnormalities, macroangiopathy disease and atherosclerosis is less clear. Retinopathy and venular dilatation appear to be associated with the presence of atherosclerosis markers (carotid plaques, intimal medial thickening, aortic calcification and aortic and popliteal plaques [10,35]). Concerning coronary artery disease, the MESA study [51] involving a multiethnic population between the ages of 43 and 84 with no cardiovascular history revealed a correlation between the presence of retinopathy (and not other retinal abnormalities) and coronary calcifications as observed by CT scan. In the same study, the reduced arteriolar calibre correlated with a diminished myocardial perfusion reserve in asymptomatic individuals with no coronary calcifications regardless of age, gender and ethnic background [52]. On the other hand, other prospective studies showed that changes in the retinal vascular calibre (and not retinopathy) were predictive of the coronary morbidity and mortality, specifically the data in the Blues Mountains Eyes Study [53,54], ARIC [55] and Cardiovascular Health Study [56]. This association appears to be more significant in women [55] and those under the age of 75. This association between retinal microvascularisation abnormalities and the incidence of cardiovascular events (coronary artery disease, cardiac insufficiency and cardiovascular mortality) is more obvious in diabetic individuals [57–59]. Nevertheless, this relationship may also be secondary to a microvascular condition. The physiopathological explanation behind the association of retinopathy and coronary calcifications on the one hand, and retinal vascular caliber and morbid-mortality on the other, is not clear.
Conclusion

Retinal microcirculation abnormalities are widely observed in the general population and include several lesions of which the main ones are retinopathy, reduced arteriolar diameter, and increased venular calibre with a perceptibly different physiopathological mechanism. The abnormalities observed in retinopathy seem to reflect disorders of the retinal vascular wall, endothelial dysfunction and inflammation secondary to diabetes, age, hypertension, obesity and metabolic disorders. The decreased arteriolar diameter signals the presence of hypertension (current or old) and the risk of hypertension onset. Current data suggest that a genetic factor could be implicated in this relationship.

More recently, it has been revealed that an increased venulars diameter is correlated with the presence of diabetes, obesity and metabolic disorders. This association appears to be mediated partly by the presence of endothelial dysfunction and inflammation.

The relationship of these retinal abnormalities with other microangiopathy abnormalities has been observed mainly in the brain and diabetic individuals. This relationship remains more difficult to highlight in the heart. The relationship of macroangiopathy with retinal microvascularisation abnormalities remains unclear. Nonetheless, the retinal vascular abnormalities appear to be predictive of an increased coronary, and more widely, cardiovascular morbidity and mortality predominantly in individuals under the age of 75.

Markers other than the simple arteriolar diameter, which allow a better reflection of the microvascular anatomic changes such as the measurement of the wall/lumen ratio of retinal arterioles by laser Doppler flowmetry, are currently under assessment and will help further clarify these correlations [60].

References


