Hypertension and the Eye
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Abstract
The retina provides an opportunity for in vivo visualization of the microvasculature. In systemic hypertension, the retina shows characteristic progressive changes which have been termed hypertensive retinopathy. The extent of these changes correlates with increased risk of systemic cardiovascular disorders. In addition, hypertension itself is a risk factor for several ocular disorders including retinal artery and vein occlusion, anterior ischemic optic neuropathy, and microvascular oculomotor nerve palsies. Glaucoma has been associated with both hypertension and hypotension, with the implication that over-treatment of blood pressure may be detrimental to glaucomatous optic neuropathy. The retinal arteries and veins can be imaged and their diameters estimated to provide an index that may be used as a marker for systemic vascular change. Dynamic changes in vessel diameter can be recorded with video-imaging with the aim of assessing arterial stiffness, while optical coherence tomography angiography (OCT-A) provides a new non-invasive technique to assess the microvascular density. Here, we review links between retinopathy and both systemic and ocular disease, and some of the techniques for assessing retinal vessels.

Key words: Glaucoma, hypertension, intra-ocular pressure, retinal imaging, retinal perfusion, retinopathy

Hypertensive Retinopathy
The retina provides a unique opportunity to assess the systemic circulation in vivo and has long been recognized as an important site for identifying systemic vascular changes in disorders such as hypertension and diabetes. The progressive changes in the vessels occurring in hypertension are readily visible and the accompanying hemorrhages, exudates and infarcts have been described as early as 1939 in a grading system for hypertensive retinopathy by Keith-Wagener-Baker (the KWB system). More recently this has been simplified to a 3-step grading system by Mitchell and Wong, which has been suggested to be easier to apply in practice (Table 1).

The pathophysiology of sustained hypertension involves initially a vasoconstriction of the retinal arteries, followed by progressive thickening of the elastic lamina and hyaline degeneration. This may be recognized on fundoscopy as focal narrowing of vessels, arteriovenous crossing changes (referred to as “nipping or nicking”) where the hardened artery compresses the vein as it crosses with a shared adventitia, and a progressive change in the vessel wall reflectivity termed copper wiring and silver wiring. With sustained hypertension, small hemorrhages, focal areas of infarction (“cotton-wool spots” – so-called because of their white appearance), as well as lipid exudates from break-down of the blood retinal barrier occur. Lipids can form a visible “macular star” pattern. These changes occur in the inner retinal circulation which is derived from the central retinal artery. The choroid, which is the deeper vascular layer of the eye directly beneath the retina supplying the photoreceptors, derives its circulation from the long and short posterior ciliary arteries, which branch from the ophthalmic artery. In severe hypertension, choroidal changes can also occur, including choroidal infarcts (represented as Elschnig’s spots – seen as pale, yellow lesions) and pigmentation lines along the larger choroidal vessels (termed Siegrist streaks). Severe hypertension can also lead to optic disc swelling through raised intracranial pressure and optic disc ischemia – termed hypertensive optic neuropathy, and this stage has been termed “malignant hypertension.” The risk of stroke and systemic organ damage is high at this stage, as discussed below.

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Table 1: Classification of hypertensive retinopathy

| Grade | Signs |
|-------|-------|
| 1     | Generalized arterial narrowing |
| 2     | Focal narrowing and arteriovenous nipping |
| 3     | As above plus hemorrhages, exudates, and cotton wool spots |
| 4     | As above plus optic disc swelling |

B. Mitchell-Wong classification of hypertensive retinopathy

| Grade        | Signs                                                                 |
|--------------|----------------------------------------------------------------------|
| Mild         | Generalized or focal narrowing, arteriovenous nipping, copper/silver wiring |
| Moderate     | Hemorrhages, exudates, and cotton wool spots                        |
| Malignant    | As above plus optic disc swelling                                   |

While the classification of the severity of the hypertensive retinopathy provides a guide as to the severity of the likely systemic manifestations, hypertension itself is also linked to several pathological disorders within the eye, most of which are vision threatening. Therefore, recognition of hypertensive changes and the initiation or upregulation of treatment are useful for both managing the general cardiovascular health of the patient and preventing ophthalmic complications. Figure 1 shows a case of hypertensive retinopathy.

### Retinopathy and Systemic Risk

The presence of hypertensive retinopathy has been linked to increased risk of cardiovascular disease including stroke, congestive heart failure, and incident coronary artery disease.\(^{[6-10]}\) Moderate retinopathy was associated with up to 4-fold risk of stroke,\(^{[6]}\) while retinal microvascular changes indicated a higher risk of cerebral atrophy.\(^{[11]}\) The relationship of retinopathy with coronary artery disease is less clear, but several studies support an association\(^{[6,10]}\) which is not unexpected given the known association between hypertension and cardiovascular mortality. Early retinopathy signs may be more valuable in younger populations (<55 years) with an association demonstrated with target organ damage that was not shown in the older cohort of the study.\(^{[3]}\) This may be because retinopathy signs become attenuated in the elderly.

Hypertensive retinopathy has been associated with target organ damage such as renal impairment and left ventricular hypertrophy.\(^{[12,13]}\) Retinal microvascular changes have also been associated with cognitive decline, brain white matter lesions, and possibly prevalence of dementia. However, epidemiological studies pertaining to dementia have had variable conclusions, complicated by different definitions, sample cohorts, and the inclusion of both diabetic and hypertensive retinopathy in the analysis. For example, the Cardiovascular Health Study found that retinopathy was associated with dementia only in subjects with hypertension or without diabetes.\(^{[14]}\) The Rotterdam Study reported an association of retinopathy and prevalent dementia in the whole population with no difference between presence or absence of hypertension and diabetes.\(^{[15]}\) The AGES-Reykjavik Study suggested that retinopathy was associated with vascular dementia but not with all-cause dementia or Alzheimer’s Disease.\(^{[16]}\) Therefore, while it is reasonable to conclude that retinopathy reflects systemic vascular disease which may be associated with increased risk of dementia, at present it cannot be concluded that the microvascular signs are predictive or diagnostic for the disease process.

### Hypertension and Ophthalmic Disorders

#### Central and branch retinal vein occlusions

A widely recognized and common association with hypertension is the development of retinal vein occlusions, including central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO).\(^{[17-19]}\) In BRVO, the arteriovenous crossing changes provide a site for compression and focal vascular damage due to the shared adventitial sheath. These can be large quadrantic occlusions or may only involve smaller branches. CRVO affecting the main trunk of the central retinal vein at the optic nerve head produces more profound visual loss, is more likely to produce macular edema, and can produce more widespread ischemia. Many BRVOs and CRVOs will resolve spontaneously and remain non-ischemic, but both can be associated with significant ischemia increasing the risk of neovascularization, with secondary retinal and vitreous hemorrhage, and eventual neovascular glaucoma. Ischemic CRVO is the most problematic and often requires pan-retinal photocoagulation and intravitreal anti-vascular endothelial growth factor (VEGF) injections. While clinical trial evidence is lacking for anti-hypertensive therapy providing an improved prognosis, to reduce the risk of occurrence in the fellow eye, it is recommended that subjects have a full cardiovascular work-up as several other systemic risk factors are involved.
factors have been associated with vein occlusions, including hyperviscosity.\textsuperscript{[15]}

**Central and Branch Retinal Artery Occlusions**

Central retinal artery occlusion (CRAO) is increased in subjects with hypertension,\textsuperscript{[20]} and it is associated with a high risk of subsequent systemic events, including stroke and acute myocardial infarction.\textsuperscript{[21]} A CRAO requires referral for immediate vascular work-up, and as these subjects often have co-existent silent ischemic infarcts\textsuperscript{[19]} which can be detected on brain MRI. There is a high incidence of ipsilateral carotid artery disease.\textsuperscript{[22]} Embolic disease from various causes and vasculitis such as giant cell arteritis can also produce a CRAO. The subject experiences sudden, painless loss of vision and the prognosis is usually poor, although some patients can be salvaged with rapid lowering of intraocular pressure and ocular massage. CRAO may be preceded by episodes of transient visual loss (amaurosis fugax). The classic clinical finding is the "cherry red spot" at the macula representing the preserved choroidal circulation, while the retinal circulation is markedly reduced or absent, with associated retinal edema. Patients with a cilio-retinal artery may preserve some central vision. There is an increased risk of neovascularization in CRAO, so patients need to be monitored for this, although the risk seems to be less than for ischemic CRVO.

Branch retinal artery occlusions (BRAO) are very frequently associated with emboli. The prognosis for BRAO is better than CRAO in that most will not have significant vision loss unless the residual scotoma is in the paracentral region. However, these subjects also have a higher risk of stroke and mortality due to their risk of embolic disease,\textsuperscript{[23]} they should undergo carotid and cardiac assessment.

**Anterior Ischemic Optic Neuropathy (AION)**

Non-AION is a frequent cause of sudden vision loss in people older than 50 years of age. The exact mechanism is not known but it is associated with systemic hypertension\textsuperscript{[24]} and is more prevalent in anatomically small crowded discs\textsuperscript{[25]} ("the disc at risk"), where disc swelling secondary to ischemia leads to infarction of a sector of the optic nerve head, often involving the lower or upper half of the optic disc, producing altitudinal visual field loss. There are no effective treatments for the condition\textsuperscript{[26]} but it does seem to be self-limiting. Patients with at-risk discs should be advised to monitor their blood pressure and other cardiovascular risk factors carefully.

**Retinal Macroneurysm**

Retinal arterial macroneurysm is a saccular dilation of a larger retinal arteriole usually within the first three bifurcations.\textsuperscript{[27]} It is associated with systemic hypertension in 60–75% of cases.\textsuperscript{[27,28]} It is often self-limiting with spontaneous thrombosis and resolution of the aneurysm, but it can be associated with sudden intra-retinal and pre-retinal hemorrhage, exudation, and associated macular edema. The edema may be chronic in up to a third of cases.

**Glaucoma**

Glaucoma represents a group of disorders that are characterized by progressive retinal ganglion cell loss with excavation (cupping) of the nerve head, producing visual field loss and eventual blindness. The two main sub-types are primary open angle glaucoma (POAG) which is a slow chronic disease, and angle closure glaucoma (ACG) which is associated with sudden onset and extremely high intraocular pressure (IOP). The common causative factor in both is raised IOP, but a large proportion of POAG patients never manifest IOP outside the normal range (often termed normal tension glaucoma – NTG), and many patients progress despite IOP lowering. It was, therefore, proposed that vascular factors may play a role in glaucomatous damage.\textsuperscript{[29,30]} It appears likely that both hypertension and hypotension may be implicated.\textsuperscript{[31]} Hypertension can cause long term damage to vessels and impaired autoregulation. Hypertension has been linked to glaucoma prevalence and to raised IOP,\textsuperscript{[32-34]} although some studies have found contradictory results.\textsuperscript{[35]} On the other hand, hypotension can lead to reduced ocular perfusion pressure (the difference between IOP and mean blood pressure) which could adversely affect the optic nerve.\textsuperscript{[36]} In fact, reduced ocular perfusion pressure has now been accepted by the World Glaucoma Society as a risk factor in their Consensus document on ocular blood flow.\textsuperscript{[36]} A major problem with many of the studies is they use blood pressure as a continuous variable, whereas there may be different phenotypes of glaucoma manifesting different pathophysiological processes at either end of the blood pressure scale. It has also been reported that systolic blood pressure variability is a more important parameter in POAG.\textsuperscript{[37]}

Several major clinical studies have looked at vascular risk factors in the development of glaucoma. The Early Manifest Glaucoma Treatment Study found lower systolic perfusion pressure, lower systolic BP, and cardiovascular disease as predictors of progression.\textsuperscript{[38]} The Barbados Eye Study found that low systolic BP and low ocular perfusion pressure doubled the risk of OAG incidence.\textsuperscript{[39]} The Egna-Neumarkt Eye Study found an association between hypertension and glaucoma but also that lower diastolic BP increased risk. There was no relation to other systemic vascular disease.\textsuperscript{[40]} The Rotterdam Study determined lower diastolic BP a risk factor, especially in treated hypertension,\textsuperscript{[41]} but its most recent report did not find any clear link with progression.\textsuperscript{[42]} The Singapore Epidemiology of Eye Diseases Study found that low systolic ocular perfusion pressure was associated with POAG and this association was in part secondary to low systolic blood pressure and high IOP.\textsuperscript{[43]}

The Los Angeles Latino Eye Study\textsuperscript{[44]} reported hypertension increased risk ratio (systolic 2.0 and diastolic 2.5) while
hypotension did also (low diastolic BP 1.6, low systolic perfusion pressure 2.9, and low diastolic perfusion pressure 2.0). They produced a U-shaped curve for glaucoma prevalence based on BP with the lowest point at normotensive levels. A similar curve was produced by Zhao et al. in their meta-analysis of glaucoma and BP[53] and recently confirmed for both systolic and diastolic BP in the National Health and Nutrition Survey study.[46]

There is a recognized normal diurnal curve of BP, with a 10% reduction at night considered physiological, usually around 2.00–4.00 am.[46,47] In the mid 1990’s, studies by Graham[46] and Hayreh[49] using ambulatory BP monitoring (ABPM) suggested that subjects with greater nocturnal dips were more likely to have glaucoma and more likely to show visual field progression.[50] This raised implications for anti-hypertensive therapy, as certain anti-hypertensive agents may have a profound effect on nocturnal blood pressure and exacerbate the fall in BP. Since IOP is known to elevate at night in the supine position the combination would lead to reduced ocular perfusion pressure at night. Many studies[43] have associated large dips in blood pressure with both POAG and normal tension glaucoma.[51–54] Bowe et al. conducted a meta-analysis[55] of all studies reporting on 24 h ABPM in glaucoma and found a consensus of progressive glaucoma in those with larger nocturnal dips of blood pressure. The odds ratio for deteriorating visual fields over 2 years with nocturnal dips of >10% in systolic or diastolic BP was 3.32 (1.84–6.00) and 2.09 (1.20–3.64), respectively.

While there is no dispute that treating hypertension is important, there may be potential adverse consequences in glaucoma from over-treating BP. The Systolic Blood Pressure Intervention Trial (SPRINT) found that a systolic target of <120 mmHg was more protective of cardiovascular complications than the conservative target of 140 mmHg.[56] However, in aiming for this there may be less margin for error, potentially pushing down the perfusion pressure in the eye to levels that could be detrimental in certain individuals, such as those with poor autoregulatory capacity. Notably, there were more episodes of hypotension and syncope in the lower target group. The more recent guidelines for hypertension therapy use stricter cutoffs; the 2017 American College of Cardiology recommending a target of <130/80 for most hypertensive patients.[57] Given the potential for nocturnal hypotension particularly when medications are taken at night,[58] we recommend checking ABPM in glaucoma patients aiming for this stricter BP therapeutic target and in patients with progressive glaucoma despite reasonable IOP control. These recommendations have also been suggested by Leeman and Kestelyn.[59]

**Association with Diabetic Retinopathy**

The retinal changes occurring in diabetic retinopathy, which like hypertensive disease also include hemorrhages, exudates, and cotton wool spots, may be exacerbated by the presence of systemic hypertension, likely through enhanced damage to retinal capillary endothelial cells and impaired autoregulation.[60] In several early studies, hypertension was demonstrated as an independent risk factor[61–63] for progression of retinopathy. In the Beaver Dam Study, higher systolic blood pressure was also associated with increased diabetic macular edema. The UK prospective Diabetes Study[64] proposed that patients with tighter BP control, defined as <150/85 mmHg, showed a 34% reduction in diabetic retinopathy progression and were less likely to need laser photocoagulation for their retinopathy. However, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study,[65] which specified even tighter BP control, did not show any additional benefit on progression of diabetic retinopathy. Laboratory studies demonstrate hypertension may enhance VEGF release[65,66] which is a stimulus for neovascularization – a feature of proliferative retinopathy. However, a recent Cochrane review[67] concluded that while there was evidence of blood pressure control reducing the 5 years incidence of diabetic retinopathy, there was less evidence to support treatment of hypertension specifically as a means of minimizing progression and macular edema.

Of note, both hypertension and diabetes are also risk factors for microvascular cranial nerve palsies, particularly 3rd and 6th cranial nerves supplying innervation to extraocular muscles.[68]

**Vascular Imaging and Grading Techniques**

Retinal imaging techniques allow for the detection and monitoring of hypertension associated ocular vascular changes. Traditional fundus photography and more recent advances in imaging technologies such as dynamic vessel analyzer, optical coherence tomography, and optical coherence tomography angiography have allowed for quantitative analysis of retinal structural and vascular changes in response to hypertension.

Analysis of retinal vascular changes relies on indices derived from either static or dynamic imaging. Static indices, such as central retinal artery equivalent (CRAE), central retinal vein equivalent, and the arteriovenous ratio (AVR), utilize analysis of fundus images to indicate retinal vascular caliber. Using the Parr-Hubbard formula, CRAE and CRVE can be calculated using artery and vein diameters in an annulus 0.5–1 disc diameter from the rim of the optic disc. The CRAE has been shown to be significantly narrower in hypertensive patients compared to non-hypertensive controls.[69–72] The link between hypertension and CRVE is less clear with some studies reporting venular dilation in hypertensive patients,[73] whilst other studies have reported that venular caliber is reduced in hypertensive patients compared to non-hypertensive controls,[74] or has no association.[72]

**Adaptive optics**

Adaptive optics have enhanced the potential resolution of standard fundus imaging to allow for qualitative and quantitative assessment of retinal microvasculature utilizing opto-electronic technology.[75] Using this technology, it has been possible to more accurately determine the wall to lumen
ratio of retinal arteries in hypertensive patients and to establish that hypertension correlates with an increase in the wall to lumen ratio\(^{[75,76]}\) compared to non-hypertensive subjects. Furthermore, Rosenbaum et al.\(^{[76]}\) reported that short-term use of antihypertensives in hypertensive patients resulted in a decrease in the retinal arterial wall to lumen ratio which was attributed to an increase in arteriolar internal diameter as there was no change to wall thickness.

**Optical coherence tomography (OCT) and OCT-angiography**

OCT is a non-invasive retinal imaging technique that provides high resolution cross-sectional images of the retina and is now widely used to document retinal and optic nerve pathology in vivo. OCT utilizes infra-red light to penetrate the retina and the backscattered light is used to produce high resolution images of the retinal layers and microstructure. Using spectral domain OCT, evidence of retinal thinning has been reported in patients with hypertension.\(^{[77-79]}\) The average thickness of the central macula, peripapillary retinal nerve fiber layer, and ganglion cell/inner plexiform layer was significantly reduced in patients with chronic hypertension both with and without clinical signs of retinopathy.\(^{[77,78]}\) These changes are believed to be due to the chronic ischemia resulting from retinal microvascular changes that occur in hypertension.

OCT-angiography (OCTA) is a newer technique that allows for non-invasive visualization of the retinal vasculature without the need for contrast dye. This technique uses motion detected during the OCT scan capture to produce high resolution images of the retinal and choroidal vasculature. Further analysis of the OCTA images allows for quantification of vessel density, perfusion density, and the size of the foveal avascular zone. Studies utilizing OCTA have reported that hypertension results in a significant decrease in retinal vessel density particularly in the deep vascular plexus, decreased perfusion density, and a significant increase in the foveal avascular zone.\(^{[78,40]}\) These results suggest that OCT and OCTA could prove to be useful tools for non-invasive monitoring of hypertension induced vascular changes. In glaucoma defects in the inner capillary network are identified in areas of nerve fiber damage \(\) Figure 2. Longitudinal studies may determine whether this capillary vascular dropout precedes nerve fiber and retinal ganglion cell loss (implying a potential causative role in damage) or in parallel secondary to reduced demand.

**Dynamic Vascular Recording**

The Dynamic Vessel Analyzer (DVA; Imedos Systems UG, Jena, Germany) software allows for analysis of dynamic changes in the diameter of retinal vessels from video. The eye tracking software helps to maintain a steady image of the retinal vessels at the optic nerve head to allow for detailed analysis of arterial and venous pulse amplitude – Figure 3 showing a frame from DVA video recording with vessels labeled and corresponding trace. With this technique the vascular dilation response to light stimulus
can be measured, and arterial and venous pulse amplitudes estimated. Using DVA analysis of video, Tong et al. reported and association between increased apnea-hypopnea index and attenuated retinal vascular pulsatility in addition to decreased CRAE and AVR.\textsuperscript{[81]}

**Potential for measuring retinal pulse wave velocity**

Pulse wave velocity (PWV) indicates the speed with which the pulse wave travels along an artery. There is a well-established association between PWV in larger arteries and arterial stiffness; the stiffer the artery, the faster the pulse wave. A variety of techniques have been used to attempt to determine retinal pulse wave velocity in humans with values ranging from 0.4 mm/s to 600 mm/s.\textsuperscript{[82-85]} Initial studies aimed at determining retinal PWV used fluorescein angiography,\textsuperscript{[86]} while more recent studies utilized the DVA,\textsuperscript{[82,83]} swept source OCT,\textsuperscript{[84]} and spectral domain OCT.\textsuperscript{[85]} Although these studies vary greatly in the reported retinal PWV values, each of the techniques detected an increased velocity in older or hypertensive subjects compared young or normotensive control subjects. Using the DVA, Rezaeian et al. demonstrated that retinal PWV correlated with carotid-femoral PWV in elderly patients suggesting that remodeling of the retinal microvasculature mimics that observed in larger vessels.\textsuperscript{[87]} Such findings warrant further studies to determine if retinal PWV can be used for determining arterial stiffness in vivo and if it could be utilized for screening or monitoring of systemic cardiovascular changes.

**Summary**

Hypertension induces characteristic retinal vascular changes which can be visualized and measured non-invasively. These changes correlate with systemic vascular disease and risk. Hypertension can also be associated with several vision threatening ocular disorders and so should be identified and managed in consultation between the ophthalmologist and the treating physician. In glaucoma both hypertension and hypotension may be risk factors, the latter from over-treatment with anti-hypertensives.

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