Chapter

Retinal Vascular Implications of Ocular Hypertension

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Abstract

In this chapter, we review the basics of retinal vascular anatomy and discuss the physiologic process of retinal blood flow regulation. We then aim to explore the relationship between intraocular pressure and retinal circulation, taking into account factors that affect retinal hemodynamics. Specifically, we discuss the concepts of ocular perfusion pressure, baro-damage to the endothelium and transmural pressure in relation to the intraocular pressure. Finally, we demonstrate the inter-relationships of these factors and concepts in the pathogenesis of some retinal vascular conditions; more particularly, through examples of two common clinical pathologies of diabetic retinopathy and central retinal vein occlusion.

Keywords: retinal hemodynamics, baro-damage, ocular perfusion pressure, diabetic retinopathy, central retinal vein occlusion, blood flow

1. Introduction

The retina shares similar anatomical features and physiological properties with other end organs such as the brain and the kidney, namely the presence of blood–brain, blood-kidney and blood-retina barrier as well as non-anastomotic end arteries [1]. Retinal fundoscopy and digital imaging have allowed for retinal microvascular abnormalities to be directly and non-invasively identified and studied as a means of better understanding the manifestation of systemic microcirculatory disorders.

Although not yet completely understood, hemodynamic factors such as perfusion pressure, blood viscosity, vascular resistance and the variations on vessel caliber that ensue, determine the blood supply and flow to the retina. By understanding these processes and their disturbances, we can better characterize the pathological processes that occur in many ocular and systemic diseases such as glaucoma, age-related macular degeneration and diabetic retinopathy, to name a few.

Retinal hemodynamics are influenced by a number of factors. Blood flow, arterial and venous pressure, vascular resistance, and blood viscosity all play important roles. Our understanding of their inter-relationship is derived from concepts used in fluid flow systems borrowed from engineering and from other physiologic studies of blood flow. Mathematically, this relationship is often simplified into Poisseuille's equation, which we will discuss more in detail in the diabetic retinopathy section. However, it is important to know that Poisseuille's equation is used mainly for Newtonian fluid in a system with laminar flow. In the retinal arterioles, the flow is often turbulent; and blood itself is not truly a Newtonian fluid. In this chapter, we will not delve into the detailed discussions of mathematical modeling,

but will only use them to better understand the hemodynamics and its biologic consequences.

Clinical evidence for the relationship between intraocular pressure (IOP) and retinal hemodynamics remains inconsistent and difficult to interpret. The reasons are two-fold. Firstly, it is difficult to capture the data of multiple variables that may contribute to hemodynamics in a clinical setting. Second, in a complex system such as retinal circulation, many variables act as both dependent and as independent variables in many feed-back loops. Moreover, these feed-back loops may vary depending on the underlying disease processes in individuals with multiple co-morbidities [2, 3].

2. Blood supply to the posterior segment

2.1 Retinal blood supply

The metabolic demands and the oxygen requirement of the retina are met by two distinct vascular systems. The inner two thirds of the retina is supplied by inherent intra-retinal vessels, fed by the central retinal artery, and drained via the central retinal vein. The photoreceptors and outer one third of the retina are supplied by the choroidal circulation [4]. Both of these supplies originate from the ophthalmic artery, which itself is a branch of the internal carotid artery.

The central retinal artery traverses through the orbital portion of the optic nerve, entering the optic disc through the lamina cribrosa. At the optic nerve, there is a combination of choroidal and retinal arterial circulation, details of which are dealt with in other chapters. The central retinal artery branches into four principal intra-retinal arteries. These further bifurcate into increasingly smaller arterioles, feeding eventually into a capillary bed as they extend towards the peripheral retina (**Figure 1**).

These capillary beds form interconnecting networks linking terminal branches of pre-capillary arterioles and post-capillary venules. Although in the juxta-papillary region this is arranged in three layers, the peri-macular region has two layers; a superficial layer located in the nerve fiber and ganglion cell layers and a second, deeper layer in the inner nuclear and outer plexiform layers. With the exception of a small avascular rim, both superficial and deep plexi reach almost to the edge of the human retina [6, 7]. The fovea is also avascular, receiving adequate oxygenation via the choroidal circulation [8].

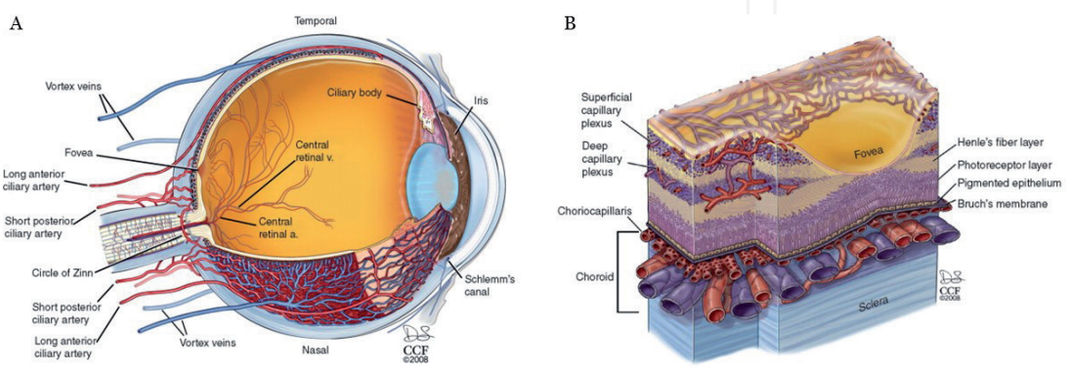

Figure 1.
(A) Sagittal drawing of the human eye showing the retinal and choroidal circulation of the left eye. (B) Cross-sectional drawing of the retinal and choroidal vasculature at the level of the fovea. Adapted from Anand-Apte and Hollyfield with drawings by Dave Schumick [5].

Post-capillary venules feed back into the superior and inferior hemi-central retinal veins, eventually uniting into the central retinal vein which centralizes at variable depths within the optic nerve eventually draining into the cavernous sinus.

The neighboring endothelial cells lining the retinal vasculature form tight junctions. Together with pericytes, they form a highly selective semi-permeable border that prevents solutes in the circulating blood from non-selectively crossing into the interstitial space within the neuroretina, constituting the inner blood retina barrier.

2.2 Choroidal blood supply

The choroid has approximately 80% of the total ocular blood supply relative to iris-ciliary body and retina [9] and consists of three distinct layers of gradually decreasing vessel caliber; Haller's layer comprises the outer, larger sized vessels, Sattler's layer is intermedial with medium-sized vessels, and the deeper choriocapillaris contains vessels with the smallest diameter [10]. The anterior choroid is supplied by the long ciliary arteries, whereas the posterior choroid is supplied by the short posterior ciliary arteries. The entire choroid drains into the vortex veins [11].

Unlike the retinal vasculature, choroidal capillaries are fenestrated, allowing free passage and exchange of intravascular contents and interstitial space, including macromolecules and cellular components. It is the monolayer of retinal pigment epithelial cells, with tight junctions at the apical aspect, that form the outer blood-retinal barrier (**Figure 1**).

2.3 Blood supply to the optic nerve head

The blood supply to the optic nerve head is complex, deriving from both the central retinal artery and from the choroid through the short posterior ciliary arteries. It has been specifically discussed in an earlier chapter in this book.

3. Blood flow within the posterior segment

3.1 Retinal blood flow

The human retina is a metabolically demanding tissue. Tissue damage and cell death can be brought about by small alterations in oxygenation or blood flow; hypoperfusion leads to hypoxia and ischemic damage; [12] whilst hyperperfusion and/or high oxygen tension leads to formation of reactive oxygen species, leading to oxidative damage [13]. Retinal blood flow must necessarily be highly regulated, and is dependent on the relationship between perfusion pressure and local resistance [11].

Under physiological conditions, retinal arterial pressure is more or less equal to mean arterial blood pressure and retinal venous pressure is more or less equal to the IOP. The difference between these pressures constitutes the driving force propelling blood through ocular capillary beds. In general, mean ocular perfusion pressure (MOPP) is positively correlated with arterial blood pressure and negatively correlated with IOP [14].

MOPP, defined as the difference between two-thirds of the mean arterial pressure (MAP) and the IOP, is a clinically modifiable factor in diseases such as Diabetic retinopathy (DR) where there is altered tissue perfusion. This will be reviewed in more detail later in the chapter.

The normal retinal hemodynamic response to increases in perfusion pressure is an increase in vascular resistance, [15] otherwise referred to as the myogenic

response. This behavior is intrinsic to smooth muscle cells such as those that line retinal arterioles and is independent of metabolic and hormonal influences.

3.2 Choroidal blood flow

Whilst retinal blood flow is characterized by a low perfusion rate, a high vascular resistance and a high oxygen extraction, the choroid, by contrast, shows a low vascular resistance, high perfusion rate and low oxygen extraction [11]

4. Regulation of blood flow in the posterior segment

4.1 Retinal blood flow regulation

Ordinarily, blood flow is regulated in response to changes in perfusion pressure and tissue oxygen tension.

Retinal circulation differs from blood flow in other non-neural systems in that local neural activity can evoke localized changes in blood flow. This behavior, termed neurovascular coupling, has been observed in the retina [16, 17] and is an emerging area of research in glaucoma [18].

More importantly, the regulatory effect of perfusion pressure on blood flow is blunted through the process of autoregulation. That is, the retinal blood flow, like that of the blood flow in the brain, is maintained or stabilized through a wide range of variations of perfusion pressure. Previous studies have shown that retinal autoregulation is adequately compensated in experimental elevations of IOP up to 29 mmHg, [19] whilst the retinal vasculature behaves more passively for greater increases in IOP [20]. This autoregulatory response is also noted in incidences of increased perfusion pressure such as periods of dynamic and static exercise; where a rise in perfusion pressure of up to 34% rise results in a rise in flow of only 4–8% [21, 22]. Teleologically, autoregulation is a protective mechanism to maintain a steady blood flow to the retina

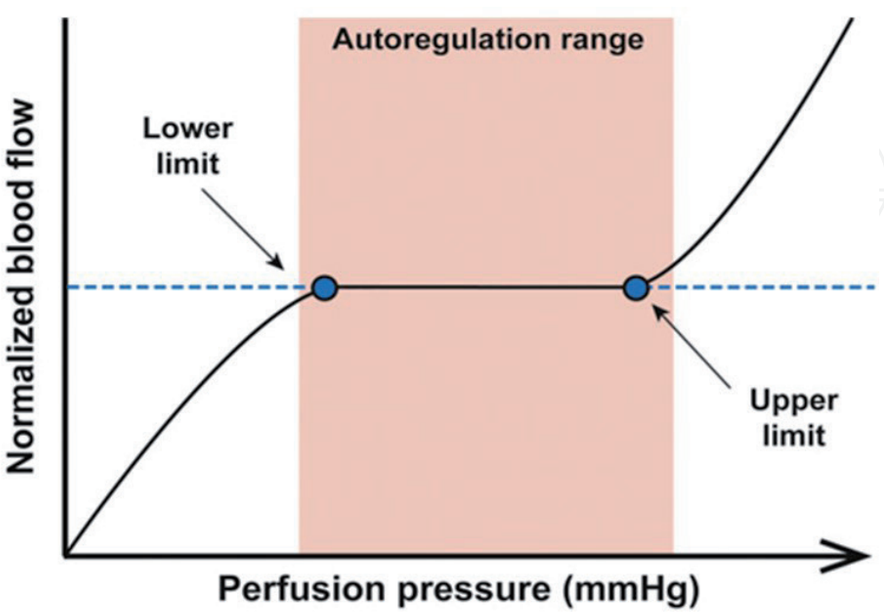

Figure 2.
Schematic of blood flow autoregulation in the eye. When fluctuations in ocular prefusion pressure exceed the autoregulation range defined by this plateau, vasomotor adjustments are incomplete and blood flow changes passively as ocular perfusion pressure changes. Figure adapted with permission from Wareham and Calkins [18].

to satisfy its metabolic demands which changes very little as compared to the wide swings of systemic blood pressure and even diurnal variations of IOP.

The autoregulation curve (**Figure 2**) shows how blood flow changes in response to ocular perfusion pressure. The curve includes a plateau region across a range of ocular perfusion pressures where the blood flow is fully compensated by the above mentioned autoregulatory mechanisms.

4.2 Choroidal blood flow regulation

Choroidal blood flow regulation is distinctly different from that of the retina; [23]. Firstly, the choroidal vascular bed is extensively innervated [24] though only partly autoregulated. There is little to no oncotic pressure gradient between intra- and extravascular spaces within the choroid due to capillary fenestration. This lack of oncotic pressure coupled with the absence of lymphatic vessels, allows for the onset of choroidal effusion if the IOP drops below a certain level.

5. Effect of intraocular pressure on retinal hemodynamics

The high metabolic and oxygen demand posed by retinal tissue is met by maintaining a steady blood flow. IOP is a major determinant of both retinal vascular perfusion pressure as well as vascular transmural pressure.

Over the past two decades, elegant mathematical modeling has been used to assess the effect of IOP elevation on the lamina cribrosa [25–27] and on arteriovenous distribution within the retinal microvasculature [28, 29].

Clinical evidence of the impact of IOP on retinal blood flow and velocity is inconsistent. Whilst several clinical studies have shown that as IOP increases, retinal and retrobulbar blood flow decreases, [30–32] others have not found this to hold true in various settings including post-operative trabeculectomy patients [33] and in patients treated with IOP lowering medications [34–36]. These inconsistencies are likely due to numerous factors, including arterial blood pressure and blood flow autoregulation [2] and the intrinsic difficulty of evaluating the individual contribution of these factors in a clinical setting. In organs where autoregulation is maintained, perfusion pressure is a weak parameter in altering blood flow within that organ.

In disease conditions, when autoregulation is disturbed, or absent, perfusion pressure as a determinant of blood flow becomes paramount. The role of arterial pressure and IOP can be easily understood in the following ways;

1. When the perfusion pressure is too high, there will be increased blood flow as well as increased transmural pressure within the retinal vasculature. This leads to endothelial damage (baro-damage) and the breakdown of the blood-retinal barrier. The endothelial damage, together with increased transmural pressure, leads to exudation and extravasation of blood products, causing retinal edema. Clinically, this series of events can be caused by an acute rise in blood pressure such as seen in malignant hypertension. It can also be seen after ocular filtration surgery when there is a significant reduction in IOP outside the range of autoregulation. In hypotony maculopathy, for example, we may often note optic disc swelling and tortuous vessels, and also macular edema and subretinal fluid, albeit more rarely.

2. Conversely, when the perfusion pressure is too low, the blood flow will fall below that required to maintain retinal metabolic and oxygen demand, thus leading to ischemia. This is seen in a number of examples:

i. In acute central retinal artery occlusion (CRAO) when an embolus blocks the retinal circulation of the central retinal artery at the optic disc thus leading to reduced blood flow and therefore widespread retinal ischemia. Anecdotal evidence from clinical experience has shown that reducing the IOP may aid in reversing the occlusion, such as when performing an anterior chamber paracentesis to rapidly reduce the IOP [37].

ii. In some patients with aortic stenosis or with carotid artery occlusion, perfusion pressure at the optic nerve head can become significant lower and fall outside the autoregulatory range. Any variations in systemic blood pressure or IOP may then cause a large enough drop in blood flow within the retinal vasculature, leading to ischemic damage to the retina ranging from mild form such as paracentral acute middle maculopathy (PAMM) or severe ischemia such as CRAO.

Furthermore, the picture may be complicated in cases where a state of low perfusion is maintained at the limits of autoregulation on a more chronic basis. Here there is no sudden event causing an ischemic infarct such as is seen in CRAO or PAMM, but rather there may be enough persistent venous stasis to induce a clinical picture reminiscent of Central retinal vein occlusion (CRVO), in a condition commonly known as Ocular ischemic syndrome or venous stasis retinopathy.

6. Effect of ocular hypertension in clinical retinopathies

The effect of IOP in retinal vascular diseases is well documented. Ocular hypertension (OHT) is a risk factor for the development of CRVO. On the other hand, OHT seems to have a protective effect on the development and progression of DR.

6.1 Retinal vein occlusions

Retinal vein occlusion (RVO) is one of the most common retinal vascular disorders, with a prevalence as high as 4.6% in adults 80 years or older, [38] and can be seen in the central retinal vein (CRVO) or in branched veins (BRVO). Although the underlying mechanisms governing RVOs are multifactorial, Virchow's triad teaches that a combination of blood flow stasis, endothelial cell damage and hypercoagulability leads to thrombosis [39].

In CRVOs, the proximity of the central retinal vein and artery (enveloped in a common fibrous tissue) to one another within the optic disc means that the presence of arterial disease such as systemic hypertension and arteriosclerosis, can predispose the central retinal vein to a pre-morbid low flow state. Additional risk factors for RVOs include coagulation disorders and hyper viscosity states, but one of the most frequently encountered risk factors is glaucoma/OHT. In BRVOs, hemodynamic changes occur at arteriovenous crossings coupled with altered blood flow thus leading to localized venous compression [40].

Verhoeff first described the relationship between glaucoma and CRVO in 1913, where he postulated that increased IOP compresses and collapses the wall of the central retinal vein, leading to intimal proliferation within the vein [41]. Whereas primary open angle glaucoma (POAG) is a feature which precedes CRVO in between 10 and 40% of patients, [Larsson] the prevalence of POAG in BRVO appears to be less frequent at between 6 and 15% [42, 43].

Many studies have analyzed the relationship between glaucoma and RVO risk, with contradictory outcomes. Yin et al. recently performed a meta-analysis of

research conducted between 1977 and 2015, examining the relationship between glaucoma and RVO and found glaucoma to be a core risk factor for RVO in 15 studies with high methodological quality [44]. The studies reviewed have suggested a number of different potential hypotheses;

- Some have considered that glaucoma and RVO are both manifestations of an underlying vascular abnormality or vascular dysregulation. Both conditions share similar risk factors; hyperlipidemia, smoking habits, abnormal plasma viscosity and inflammatory activity [45–47]. Other abnormalities found with raised fibrinogen and IgA are also consistent, implying that associated medical conditions are of greater significance to deterioration in RVOs rather than the presence of glaucoma or OHT itself.

- POAG has been found to precede vascular occlusion [48–51] and disc hemorrhage is frequently seen in POAG patients in the clinic, leading to the hypothesis that RVO and POAG might share a common pathogenesis [52].

- In patients with compromised retinal circulation and autoregulatory mechanisms, a minor rise in IOP may be high enough to reduce ocular blood flow sufficiently to propagate stagnant blood flow. This hypothesis is supported by the finding of a reduction in IOP thresholds, normally estimated to be 27-30 mmHg in patients with chronic simple glaucoma, up to which autoregulation, by increasing arterial pressure with decreased vascular resistance, maintains normal blood flow [53].

- Some groups have presented a vascular hypothesis of glaucoma; [54] individuals with primary angle closure glaucoma as well as POAG are known to have narrower retinal arteries and veins than normal subjects [55]. Therefore elevated IOP may lead to greater vessel wall compression in these "primed" vessels, leading to vein intimal proliferation and collapse of retinal capillaries [56, 57].

Although glaucoma and OHT are risk factors for CRVO, once CRVO is established, there is a curious phenomenon of lowered IOP in the eye with the RVO as compared to the fellow, non-affected eye. The exact cause of this lowering of IOP is not understood, though Hayreh et al. postulated it may be due to the release of soluble factors induced by relative ocular ischemia [58].

This lowered IOP, combined with increased venous pressure, increases the capillary hydrostatic pressure according to Starling's Law [59]. This in turn leads to increased leakage from compromised endothelial cells; the clinical presentation of which is seen as macular edema and hemorrhagic retinopathy.

In fluid dynamics, Bernoulli's principle states that an increase in the speed of a fluid (kinetic energy) occurs simultaneously with a decrease in static pressure or a decrease in the fluid's potential energy. The converse is the case in severe CRVO where the venous thrombosis causes significant slowing down of blood flow velocity, the kinetic energy that drives the blood flow forward within the capillary network can be reduced enough to cause intra capillary thrombosis, as evidenced in wide spread capillary drop out on fluorescein angiography. When enough retinal area is involved (usual criteria is 10 disc areas on angiography), the resulting ischemia may lead to neovascular complications. This is referred to clinically as ischemic CRVO. At the same time, according to Bernoulli principle of total energy conservation, the decrease in kinetic energy will result in a commensurate increase in the potential energy as expressed in lateral or transmural pressure. This increase in lateral pressure causes extravasation of fluid into the interstitial space and results in retinal edema.

Whilst our current approach to the management of RVO incorporates addressing associated systemic risks common to both glaucoma and RVO, further work is needed to establish the exact effects of elevated IOP as well as the additional effect of glaucoma medications on the autoregulatory capacity of retinal blood flow e.g. timolol enhancing autoregulation and thus possibly aiding perfusion following RVOs [60].

6.2 Diabetic retinopathy

DR continues to be one of the leading causes of blindness globally, and as retinal capillaries can be visualized directly, the progression of DR can be continuously assessed. The microangiopathic processes noted in the retina are echoed in the glomeruli of diabetic patients. The glomerular microcirculation has received significant attention as it's accessibility to both clinical and experimental observation is unique, in that fluid and macromolecule movement across capillary walls can be easily quantified [61]. Glomerular hemodynamic abnormalities, as with the microcirculation in the retina, are thought to be mediated by a complex chain of events including direct mechanical injury (baro-damage) to the capillaries, [62] and subsequent intracapillary coagulation [63]. As with renal microcirculation, hemodynamic abnormalities within the retinal microcirculation can be detected many years before DR becomes overt.

Multiple factors, including altered levels of vasoactive substances, altered vasomotor responsiveness and persistent hypoxia leads to marked venous vasodilation. Although the consequent elevations in capillary pressure and blood flow may be the inciting mechanism for the onset of diabetic microangiopathy, the factors linking hyperglycemia to vascular cell dysfunction, capillary dropout, tissue hypoxia, and abnormal angiogenesis, remain poorly described [64, 65]. Patients with diabetes are however known to have dysfunctional retinal perfusion [66] and an abnormal autoregulatory capacity [67].

The retinal microcirculation is sensitive to local variations in oxygen tension, with capillary blood flow and vessel diameter varying as necessary in response to local metabolic demand; [61] retinal capillaries dilate with low ambient oxygen tensions, and constrict with high ambient oxygen tensions [68].

As DR progresses, capillary microaneurysms, exudates and hemorrhages are seen, followed by endothelial proliferation with neovascularization. In the latter stages, focal retinal atrophy and vitreous body adhesions occur, eventually leading to tractional retinal detachment if not treated. These advancing stages of DR are characterized by local capillary basement membrane thickening, endothelial proliferation and intracapillary thrombosis, the latter of which further aggravates endothelial proliferation. This cascade results in capillary lumen obstruction, exacerbated even more so in the presence of hypoxia. Over time, retinal microvascular damage in the presence of persistent hypoxia results in elevated intraocular vascular endothelial growth factor (VEGF), an endothelial-specific diffusible factor that mediates permeability and development of vasculature.

That hemodynamic factors play an important role in the development of DR is evident in many clinical observations. Generally, disease states that cause an elevation in retinal perfusion pressure hastens the onset of DR. When retinopathy is already established, the same high perfusion state can cause a more rapid progression of the retinopathy. Conditions that cause perfusion pressure to increase include:

i. Systemic hypertension

The United Kingdom Prospective Diabetes study (UKPDS) found that improved blood pressure control decreased the progression of diabetic

microangiopathy and correlated with a reduction in risk of cerebrovascular incidents by more than a third [69].

ii. Pregnancy

It is widely recognized that pregnancy worsens during pregnancy [70–72]. DR severity pre-pregnancy, metabolic control during pregnancy and pregnancy related hypertension have all be identified as risk factors for this worsening [70, 72]. Increased cardiac output and plasma volume during pregnancy, as well as a decrease in peripheral vascular resistance significantly increase blood flow to different parts of the body, including the retinal vasculature. Chen et al. have shown that when increased blood flow was documented in the first trimester, DR progressed, in contrast to unchanging DR severity in women whose retinal blood flow remained unchanged [73]. The hyperdynamic circulatory state induced by pregnancy is counteracted effectively only if normal autoregulatory control of blood flow is maintained. In some diabetic pregnant women, these mechanisms are flawed, where increased blood flow potentially inflicts endothelial damage by inciting additional shear stress at the capillary level.

Conversely, disease state that leads to a decrease in retinal perfusion pressure may protect against the development or the progression of DR.

6.2.1 Carotid stenosis

It is noted that patients with carotid artery disease may have eyes with asymmetric severity of DR; with the less affected eye having an ipsilateral carotid artery that is more obstructed. The protective effect has been attributed to the reduction in the retinal arterial perfusion pressure [74]. It should be noted that when the carotid occlusion becomes severe, that is exceeding 90% of the vessel caliber, this protective effect is lost due to consequent ischemia [75].

6.2.2 Optic atrophy

A similar asymmetric DR severity can be seen in patients with optic atrophy. The side with optic atrophy has severe DR compared to the side with a normal optic nerve. This can be explained by the narrowing of the retinal arterioles generally seen in eyes following the onset of optic atrophy [76, 77]. In these eyes, although the arterial pressure at the optic nerve head may not be altered, the capillary perfusion pressure is much reduced due to the narrowing of the vessel caliber.

The relation between vessel caliber and end capillary perfusion pressure can be understood through Poisseuille's blood flow equation: [78].

$$\Delta p = 8\mu LQ / \pi R4 = 8\mu LQ / A^2 \quad (1)$$

where:

Δp is the pressure difference between the two ends (pressure drop) L is the length of pipe (distance blood travels to reach capillary bed) μ is the dynamic viscosity.

Q is the volumetric flow rate (blood flow).

R is the pipe radius (vessel caliber).

A is the cross section of pipe (vessel cross sectional area).

Note that the drop in perfusion pressure at the capillary level is inversely correlated to the square of the cross sectional area of the vasculature. The narrower the vessel caliber, the smaller the cross sectional area, the drop in perfusion at the capillary level is increased by the fourth power of the radius of the vessel.

6.2.3 Myopia

In patients with anisometropia where one eye is significantly more myopic than the other, it is the eye with higher myopia that demonstrates less severe DR levels [79, 80]. Myopic eyes tend to have longer axial lengths, consequently for every corresponding point in the retina, the arteriole has to travel further to reach compared to that in an eye with a normal axial length. This increased blood travel, can be simplified as having comparatively longer vessel or pipe length, with a consequent decrease in end capillary perfusion. Mathematically, we can once again understand it through Poisseuille's equation: as L increases, Δp increases also, meaning a drop in the capillary perfusion pressure.

6.2.4 Ocular hypertension and glaucoma

Whereas the clinical evidence from the above mentioned examples of asymmetric DR seems to point to the general idea that an increase in end capillary perfusion pressure is a main risk for the development or worsening of DR, studies directly examining the association between MOPP and DR are rare. Many studies have assessed the relationship between retinal blood flow and DR [81–84]. Whilst a series of studies have reported that increased retinal blood flow is associated with background DR, [81, 82] pre-proliferative DR, and proliferative DR, [81] as with RVO, data on the relationship of the effect of MOPP remains inconsistent globally. Whilst some researchers have shown higher MOPP is associated with DR, macular edema, and hard exudation, [81, 85] others did not observe this association [86].

The pathophysiology of glaucoma is not completely understood. However, both diabetes and glaucoma appear to share some common risk factors and pathophysiologic similarities, including the phenomenon of neurovascular coupling (NVC). Within the retina, studies have shown that not only is vascular dilatation reduced in patients with little to no DR, but also in glaucoma patients when compared to that in healthy subjects [87–89]. These studies indicate a process whereby abnormal neurovascular coupling precedes a visible angiopathy in humans in both glaucoma and DR.

Several population-based studies have shown a positive association between ocular hypertensive disorders and diabetes mellitus [90–92] whilst some shown a negative association [93, 94]. Becker et al. showed that glaucoma decreased the incidence of DR and postulated this was because the increase in IOP lowered the transmural hydraulic pressure gradient across retinal capillaries [95].

Some groups have postulated that the reduced number of retinal ganglion cells found in glaucoma lead to a reduced ischemic drive and thus prevents DR development [96, 97]. Singal et al. showed that the mean duration of diabetes with early non-proliferative changes was maximum in patients with primary open angle glaucoma (15.8 years), followed by normal tension glaucoma (14.0 years) and then in non-glaucomatous patients (13.3 years) [96]. They also observed that advanced stages of DR changes were seen more so in the group without glaucoma. These findings, alongside those of Williams et al., suggests that not only does glaucoma delay the onset of DR, but that glaucoma also has an effect in delaying the progression of DR changes [96, 97].

The protective effect of ocular hypertension and glaucoma on DR can also be understood through the hemodynamic changes.

Increased IOP causes a decrease in ocular perfusion pressure. This directly reduces endothelial baro-damage. Also, in patients with established glaucoma with significant optic atrophy, the resultant arteriole narrowing would additionally cause a significant increase in vascular resistance and a decrease in end capillary perfusion as demonstrated through Poisseuille's equation.

6.2.5 Pan retinal laser photocoagulation (PRP)

PRP is an effective treatment against proliferative DR. The DRS study showed that the 5 year rate of severe vision loss from proliferative DR was reduced from 50% without PRP to 20% by this treatment, as onset and progression of neovascularization was prevented. Furthermore, PRP reduced the risk of elevated IOP during the study period thus delaying onset of neovascular glaucoma [98]. It's therapeutic effect is understood to be due to the reduction of oxygen and metabolic demand through tissue ablation. It should be pointed out that after PRP, the arteriole calibers are decreased significantly, resulting in a marked reduction of end capillary perfusion pressure.

6.2.6 Anti-VEGF intravitreal injections

Development of injectable anti-VEGF agents into the eye have revolutionized the way in which diabetic macular edema and proliferative DR can be managed. Multiple pivotal trials reproducibly demonstrated significant regression of DR severity with anti-VEGF treatments, [99–101] as well as complete regression of new vessels in up to 20% of cases [102]. It has also been noted that in diabetic macular edema treatment, the number of injections needed to control macula edema decreases in the second and third year as compared to the first year of treatment [99]. These findings suggest that continued anti-VEGF, with attendant restoration of healthier hemodynamics, a reduced capillary perfusion pression and less baro-damage to the capillary endothelium may confer some improvement in the severity of retinopathy.

7. Conclusions

A comprehensive review of retinal hemodynamics, the interplay between various factors such as blood pressure, vascular resistance, IOP, ocular perfusion pressure and blood flow are covered in this chapter. Changes in one of more of these factors are discussed in different disease states. Specifically, we discussed two important and frequent clinical entities; CRVO and DR. IOP plays an important role in the pathogenesis of each of these two conditions. In eyes with predispositions to venous stasis, IOP causes a further reduction in ocular perfusion and thus exacerbates the stasis. On the other hand, in diabetic microangiopathy, the endothelium is damaged, so that an increased IOP with attendant reduction in perfusion pressure actually protects the endothelium from transmural pressure related trauma.

Conflict of interest

The authors declare no conflict of interest.

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