Pathophysiology of Glaucomatous Optic Neuropathy: Role of Optic Nerve Head Vascular Insufficiency

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INTRODUCTION

In 1970, based on my experimental and clinical studies, I defined glaucoma as: “a disease wherein the normal balance between the intraocular pressure and the blood pressure in the choroidal vessels supplying the optic disc and retrolaminar part of the optic nerve is disturbed, resulting in vascular insufficiency in the optic disc and retrolaminar part of the optic nerve, and hence in visual field defects and pathological changes in the optic disc and optic nerve.” Since the conventional wisdom at that time was that glaucoma was essentially mechanical in nature, caused solely by high intraocular pressure (IOP), this concept was received with marked skepticism. Since then, however, evidence that vascular insufficiency in the optic nerve head (ONH) plays an important role in pathogenesis of glaucomatous optic neuropathy has progressively accumulated; so that now its vasogenic origin is widely accepted.

To understand the vasogenic mechanism of glaucomatous optic neuropathy, it is crucial to have a good understanding of the following:

1. Blood supply of the ONH.
2. The various factors that influence the ONH circulation.

BLOOD SUPPLY OF THE OPTIC NERVE HEAD

The subject of the blood supply of the ONH, while crucial in understanding the pathogenesis of glaucomatous optic neuropathy, anterior ischemic optic neuropathy and other ischemic disorders of the ONH, has been beset by controversy over the decades. One of the reasons for this is the habit of extrapolating the in vivo ONH blood supply and flow pattern from postmortem cast, histological and morphological studies. All these aspects of blood supply of the ONH are discussed at length elsewhere. Briefly, from both the anatomical (Fig. 1) and blood supply (Fig. 2) points of view, the ONH consists of four distinct regions. These regions, from anterior to posterior aspect, are as follows.

The Surface Nerve Fiber Layer

This is the most anterior layer of the ONH. It contains the compact optic nerve fibers as they converge on to this part from all over the retina and bend to run back (Figs 1A). This part is essentially supplied by the retinal arterioles (Fig. 2A). In few cases, however, the temporal part may be supplied by the posterior ciliary artery circulation from the underlying prelaminar region. When a cilioretinal artery (rarely a tiny ciliopapillary artery) is present, that supplies the corresponding part of the surface nerve fiber layer.

The Prelaminar Region

This part consists of optic nerve fibers arranged in bundles, surrounded by glial tissue septa, which contain capillaries (Fig. 1B). There is overwhelming evidence that this region is supplied mainly by centripetal branches from the peripapillary choroid (Fig. 2). The blood supply in the peripapillary choroid, as well as in the ONH, is sectoral. The peripapillary choriocapillaris and central retinal artery play no role in its blood supply.

Lamina Cribrosa Region

This forms a band of dense, compact connective tissue extending transversely across the entire width of the ONH (Fig. 1A). The lamina cribrosa is anchored firmly at the periphery to the surrounding sclera, centrally to the connective tissue envelope of the central retinal vessels, and posteriorly to the septa of the retrolaminar optic nerve (Fig. 1C). It is laminar in nature, with collagen bundles alternating with glial tissue. The diameter of the openings for the nerve fiber bundles varies greatly in different parts. Quigley et al showed that there is less connective tissue and larger pores in the superior and inferior than nasal and temporal parts, and the least amount in the inferoperipheral region.
The lamina cribrosa region is supplied by centripetal branches arising directly from the short posterior ciliary arteries or from the intrascleral Circle of Zinn and Haller, when that is present (Fig. 2). In the lamina cribrosa, the blood vessels, 10 to 20 μ in diameter, lie in the fibrous septa and form a dense capillary plexus (Figs 1C), which makes this part of the ONH a highly vascular structure. The central retinal artery does not supply this region.

A combination of the facts that: (a) the sizes of the pores in the lamina cribrosa and the thickness of the septa in-between the pores vary so widely in different part of the lamina cribrosa, and (b) the septa are essential vascular bundles, may play a role in differential susceptibility of different parts of the ONH to ischemia. Thinner septa would distort much more readily than the thicker septa; that in turn would result in more distortion of the blood vessels in thinner bundles and interference with the circulation.

**Retrolaminar Region**

This part of the optic nerve lies immediately behind the lamina cribrosa. It is enclosed by dura, arachnoid and pia (Fig. 1A). Here the nerve fiber bundles lie in polygonal spaces formed by the connective tissue septa (Fig. 1D). The septa are attached in the periphery to the pia, centrally to the connective tissue envelope around the central retinal vessels, and anteriorly anchored to the lamina cribrosa. The septa are essentially vascular bundles and form a complicated intercommunicating tubular framework for the nerve fiber bundles. The nerve fibers in this part are myelinated but are unmyelinated anterior to that.

This region has centripetal and centrifugal vascular systems (Fig. 2).

a. *The centripetal system* is the main and consistent vascular system, formed primarily by the recurrent pial branches from the peripapillary choroid and the Circle of Zinn and Haller (or the short posterior ciliary arteries), with additional pial branches from the central retinal artery and maybe from other orbital arteries. Branches from the pial vessels run centripetally in the septa.

b. *A centrifugal system* may be seen in some nerves and consists of a few inconstant branches from the central retinal artery.

In summary, the primary source of blood supply to the ONH is the posterior ciliary artery circulation via the peripapillary choroid and short posterior ciliary arteries (or the Circle of Zinn and Haller, when present) (Fig. 2).
Interindividual Variations in the Blood Supply of the ONH

When dealing with the role of blood supply of the ONH in various ischemic disorders of the ONH, there is almost a universal misconception that all ischemic disorders can be explained based on one universal vascular pattern of the ONH. This has resulted in confusion and controversy. It is crucial to realize that there is no one universal blood supply pattern of the ONH; there is a marked interindividual variation in it; therefore there is marked variation in the pattern of ischemic disorders among various eyes. The subject of interindividual variation in the blood supply of the ONH is discussed at length elsewhere.3,4,13,14

Interindividual variations in the blood supply of the ONH are caused by infinite variation in the following.

i. The anatomical vascular pattern of the ONH: This varies widely.

ii. The number and pattern of distribution of the various posterior ciliary arteries: Usually there are 2 to 3 posterior ciliary arteries in an eye (Figs 3 to 6), called medial and lateral posterior ciliary arteries, but there may be 1 to 5 of them. The area supplied by each posterior ciliary artery varies widely from eye to eye (Figs 3 to 6).14

iii. The relationship of the watershed zone(s) between the posterior ciliary arteries to the ONH: Watershed zone is the border between the territories of distribution of...
Figs 3A to D: Fluorescein fundus angiograms of four eyes with nonarteritic anterior ischemic optic neuropathy showing different locations of the watershed zone between the medial and lateral posterior ciliary arteries (vertical dark band and arrow) in relation to the optic disc. (A) Right eye with the watershed zone lying temporal to the optic disc. (B) Right eye with the watershed zone passing through the temporal part of the disc and adjacent temporal peripapillary choroid. (C) Left eye with the optic disc lying in the center of the watershed zone; (D) Left eye with the watershed zone passing through the nasal part of the disc and adjacent nasal peripapillary choroid. A reproduced from Hayreh² and others from Hayreh¹³)

Fig. 4: Diagrammatic representation of some of the locations of the watershed zones (shaded area) between the medial and lateral posterior ciliary arteries in human eyes: (upper left) the shaded area represents the area within which the watershed zone may be situated. The remaining five diagrams are some examples of variations in the location. Fig. 3 shows fluorescein angiograms of some of these locations of the watershed zone (Reproduced from Hayreh¹⁴)
adjacent end-arteries. Posterior ciliary arteries are end-arteries; therefore, there are watershed zones between the various posterior ciliary arteries. The significance of the watershed zone is that in the event of a fall in the perfusion pressure in the vascular bed of one or more of the end-arteries, the watershed zone, being an area of comparatively poor vascularity, is most vulnerable to ischemia. As seen in Figures 3 to 6, ONH shows a marked interindividual variation relationship to the location of the watershed zone between the posterior ciliary arteries. This is an important factor in determining not only the vulnerability of ONH to ischemia but also the site and severity of ischemia in the ONH.

**Venous Drainage of Optic Nerve Head**

The venous drainage from the ONH is by the central retinal vein (Fig. 2B). In the prelaminar region, it also has connections with the peripapillary choroidal veins. In the event of central retinal vein occlusion behind the lamina cribrosa, this communication assumes importance in developing retinociliary collaterals (erroneously called optociliary shunts).
**Conclusions about Blood Supply of the ONH**

a. The main source of blood supply to the ONH is the posterior ciliary artery circulation *except for* the surface nerve fiber layer, which is supplied by the central retinal artery circulation. This dual supply has important implications when trying to evaluate the ONH circulation by various methods (see below).

b. The blood supply pattern in the ONH shows marked interindividual variations.

c. The blood supply in the ONH has a sectoral distribution, which is responsible for sectoral nerve fiber bundle defects in ONH ischemic disorders.

d. Location of the watershed zones between the various posterior ciliary arteries may play an important role in the development of ischemic disorders of the ONH, as well as, in determining their site and severity.

**PATHOPHYSIOLOGY OF VARIOUS FACTORS THAT INFLUENCE THE ONH CIRCULATION**

To understand the role of vascular insufficiency in the ONH in the pathogenesis of various ischemic disorders of the ONH, it is fundamental to understand the blood flow in the ONH in health and disease and the various factors that influence it. Lack of knowledge about these issues has caused most of the controversy about the pathogenesis and management of various ischemic disorders of the ONH. These factors are discussed at length elsewhere.15,16

To calculate the ONH blood flow, the following formula is used:

\[
\text{Blood Flow} = \frac{\text{Perfusion pressure}}{\text{Vascular Resistance}}
\]

**Perfusion pressure** = Mean arterial blood pressure (BP) in the ONH vessels (not in the brachial artery) minus the IOP. Perfusion pressure is also equal to mean arterial pressure minus venous pressure in any vascular bed. Normally the pressure in the central retinal vein at the optic disc is slightly higher than the IOP, so that for all practical purposes, IOP is usually considered a good index of the ocular venous pressure.

**Mean BP** = Diastolic BP + 1/3 (systolic minus diastolic BP).

Therefore, the blood flow depends upon three parameters: (1) vascular resistance, (2) BP, and (3) IOP. The pathophysiology of these 3 factors, as well as of some others that influence the ONH blood flow, is discussed at length elsewhere,15,16 and the following is a brief account.

1. **Vascular Resistance**

This, according to Poiseuille’s Law, is (a) inversely proportional to the fourth power of the radius of the vessel, (b) directly proportional to blood viscosity and (c) the length of the vessel. Therefore, vascular resistance in the ONH depends upon the state and caliber of the vessels feeding the ONH circulation and rheological properties of the blood. The latter are influenced by a large variety of hematologic disorders, particularly those causing increased blood viscosity.

The state and caliber of the vessels feeding the ONH may be altered by many factors, including the following.

**A. Autoregulation of Blood Flow**

The goal of autoregulation is to maintain a relatively constant blood flow, capillary pressure and nutrient supply in spite of changes in perfusion pressure. The evidence shows that blood flow in both the retina and ONH has autoregulation.16 Autoregulation of blood flow is due to alteration in resistance to blood flow. It is generally thought that the terminal arterioles regulate the resistance to flow, i.e. they dilate to increase the blood flow when the perfusion pressure falls, and constrict to reduce the blood flow in arterial hypertension. But since there is a limit to how far the terminal arterioles can constrict or dilate, the autoregulation operates only within a certain critical range of perfusion pressure (Fig. 7); it becomes ineffective and breaks down when the perfusion pressure goes below or above this critical range. Under those circumstances, the blood flow is directly proportional to the perfusion pressure. Thus, contrary to the general belief, the presence of autoregulation does not automatically regulate the blood flow at all levels of perfusion pressure (Fig. 7).

**Breakdown of blood flow autoregulation in the ONH:** Many systemic and local factors can cause this. The systemic causes include aging, arterial hypertension (Fig. 7), diabetes mellitus, marked arterial hypotension from any cause, arteriosclerosis, atherosclerosis, hypercholesterolemia, vasospasm and probably regional vascular endothelial disorders.17-20 It is also possible that many other, as yet unknown, causes can derange the autoregulation; possibly, also, some persons are born with...
defective autoregulation, for instance, those who suffer from orthostatic arterial hypotension for no apparent reason.

B. Vascular Endothelial Vasoactive Agents

These agents are formed by vascular endothelium. Recent studies have shown that they play an important role in modulating the local vascular tone and most probably also in blood flow autoregulation, and they also regulate platelet function, coagulation and vascular growth.\textsuperscript{21} The vascular endothelial cells release various known endothelial vasoactive agents, which include prostanoids, nitric oxide, endothelins, angiotensins, oxygen free radicals, smooth muscle cell hyperpolarization, thromboxane A\textsubscript{2} and other agents.\textsuperscript{21-24} Renin-angiotensin system also exists in the vessel wall and plays a significant part in vasomotor control,\textsuperscript{25-29} apart from playing an important role in the control of arterial BP. Endothelium also plays a role in regulation of fibrinolysis because plasminogen activators and inhibitors are synthesized by the endothelium,\textsuperscript{30,31} and in thrombus formation by affecting the platelet aggregation, adhesion and other properties through prostacyclin, nitric oxide and other agents.\textsuperscript{21} Endothelial cells regulate vasomotor function not only by the various endothelial derived vasoactive agents but also they can function as mechanosensors and can transduce the mechanical signals produced by the physical force of blood flow into a biochemical signal to which the vessel can respond;\textsuperscript{32} this may be responsible for flow dependent changes in circulation.

Pathophysiological changes in the vascular endothelial cell structure and/or function occur in most major cardiovascular diseases, including atherosclerosis, diabetes mellitus, hypertension and ischemia.\textsuperscript{21,33-42} Vascular tone depends upon a balance between the endothelial vasodilators (e.g., nitric oxide) and vasoconstrictors (e.g., endothelin), so that reduced formation of vasodilators would result in vasoconstriction and vice versa (Fig. 8). Production of nitric oxide is impaired in several conditions, e.g., essential hypertension, ischemia and fall of arterial oxygen level.\textsuperscript{33,35,39,40-42} Therefore, endothelial cells play an important role in modulating the microvascular tone and blood flow autoregulation. As far the role of endothelial derived vasoactive agents in the ONH and ocular ischemia is concerned, a number of studies have reported the important role played by endothelin-1 and nitric oxide in modulating the local vascular tone and regulating blood flow in the ophthalmic, posterior ciliary and retinal arteries and retinal and ONH vessels.\textsuperscript{15,16} Arteriosclerosis, hypercholesterolemia, aging, arterial hypertension, diabetes mellitus, ischemia and other causes so far unknown in the regional ocular and ONH vessels may be associated with abnormalities in production of endothelial derived vasoactive agents, thereby influencing the vascular resistance and blood flow in the ONH.\textsuperscript{20} Experimental studies have shown that perineural chronic infusion of endothelin-1 on the anterior optic nerve in rabbits and rhesus monkeys produced a dose-dependent vasoconstriction, associated with a significant decrease in blood flow, increased optic disc cupping in rabbits, and diffuse loss of axons in monkeys.\textsuperscript{41-46} Thus, an understanding of the role of vascular endothelial vasoactive agents is crucial in any consideration of ONH circulation and ischemic disorders.

C. Vascular Changes in the Arteries

Feeding the ONH Circulation

Arterial changes, which alter the vascular resistance in the internal carotid artery, ophthalmic artery and posterior ciliary arteries and/or smaller vessels in the ONH itself, may be produced by vasospasm, arteriosclerosis, atherosclerosis, vasculitis, drug-induced vasoconstriction or dilatation, and a host of other systemic and cardiovascular diseases.

2. Arterial Blood Pressure

According to the blood flow formula (see previous page), perfusion pressure in the ONH vascular bed determines the blood flow in the ONH. Perfusion pressure in the ONH vascular bed in turn depends mainly upon the arterial BP in the ONH vessels. Almost invariably, the BP is measured in the brachial artery during the waking hours; that, however, does not usually reflect the BP in the ONH vessels, for the following reasons:

i. There is a progressive fall of BP from the carotid artery to ophthalmic artery, posterior ciliary artery, onto the small vessels in the ONH. So that normally the actual BP in the ONH vessels may be half or even less than that measured in the brachial artery.

ii. If there are vascular changes in the internal carotid artery, ophthalmic artery and posterior ciliary arteries and/or smaller vessels in the ONH itself (produced by vasospasm, arteriosclerosis, atherosclerosis, vasculitis, drug-induced...
Pathophysiology of Glaucomatous Optic Neuropathy: Role of Optic Nerve Head Vascular Insufficiency

vasoconstriction, or other systemic and cardiovascular diseases), then the BP in the ONH capillaries would be even much lower than in normal individuals.

ii. During sleep, nocturnal arterial hypotension lowers the BP significantly from that recorded during waking hours (Fig. 9).47-52

Thus, it is important to realize that clinical BP measurement during waking hours in the brachial artery very much overestimates the actual BP in the ONH vessels. Since clinically measured BP is invariably regarded to represent BP in the ONH, that erroneous impression has resulted in controversy of the role of BP in the pathogenesis of ischemic disorders of the ONH.

Both arterial hypertension and hypotension can influence the ONH blood flow in a number of ways.

A. Arterial Hypertension

Both chronic arterial hypertension and malignant arterial hypertension can interfere with the ONH blood flow. This may be due to a number of mechanisms in these patients, including the following.

i. In arterial hypertension, there is increased vascular resistance in terminal arterioles all over the body—the basic pathology present in arterial hypertension.

ii. Arterial hypertension produces abnormalities in blood flow autoregulation. These may be produced by a variety of factors, including the following: (a) abnormalities in endothelial derived vasoactive agents [particularly reduction in production of nitric oxide (see previous parg), (b) hypertension-induced adaptive change in blood flow autoregulation (Fig. 7),48,53 and (c) direct effect on the ONH blood flow by circulating vasoconstrictor agents (angiotensin and other circulating vasoconstrictor agents) in arterial hypertension.17,54

iii. Abnormal arterial hypotension produced by aggressive treatment of arterial hypertension. This has now emerged as a major problem with the aggressive use of highly potent hypotensive drugs currently available (see below). This may seem a paradoxical phenomenon—arterial hypertensives developing arterial hypotension, but this is a factor which is invariably overlooked when evaluating and managing ONH ischemic disorders.52

B. Arterial Hypotension

In an ONH with defective autoregulation, a fall of BP below a critical level must decrease its blood flow. A fall of BP in the ONH may be due to systemic or local hypotension.

i. Systemic arterial hypotension: The most common causes of systemic arterial hypertension are nocturnal arterial hypotension (Fig. 9)47,48,50,55 and intensive anti-hypertensive medication in hypertensives (with beta-blockers, calcium-channel blockers and/or ACE inhibitors and other highly potent hypotensive drugs).48-51 less common causes include massive blood loss or shock.56 Recent studies have shown an association between nocturnal arterial hypotension and glaucomatous visual loss.48,50,55,57-61 Nocturnal arterial hypotension also plays a role in the development of non-arteritic anterior ischemic optic neuropathy, because at least 75% of these patients discover visual loss on waking in the morning.62

ii. Local arterial hypotension: This may be due to narrowing of the regional arteries, such as the internal carotid, ophthalmic or one or more of the posterior ciliary arteries, or arterioles supplying the ONH, or a fall of perfusion pressure locally in the peripapillary choroid which supplies the ONH (Fig. 2A). As mentioned above, under such circumstances, the BP measured in the brachial artery grossly overestimate the BP in the ONH vessels.

3. Intraocular Pressure

As mentioned above, the perfusion pressure is equal to mean BP minus IOP. Thus, there is an inverse relationship between IOP and perfusion pressure in the ONH, if the autoregulation is defective. In persons with normal BP and autoregulation, a much greater rise in IOP would be required before the ONH blood flow is compromised (e.g. in ocular hypertensives). By contrast, in persons with arterial hypertension, defective autoregulation or other vascular risk factors, even “normal” IOP may interfere with the ONH blood flow (e.g., in normal tension glaucoma). That may be of importance in the
Assuming a supine position causes a short-term rise in IOP. As a part of circadian variation, the IOP is higher during sleep than during waking hours and is highest early in the morning. The recurrent spikes of raised IOP above normal levels during sleep (due to supine position and also sleep) may be completely missed during routine IOP measurement in clinic visits. However, these spikes in IOP, combined with the development of concurrent nocturnal arterial hypotension during sleep (Fig. 9), may constitute an important hidden risk factor for ONH ischemia in vulnerable ONHs. When dealing with the pathogenesis of glaucomatous optic neuropathy, this hidden risk factor is not always considered.

It has been claimed or implied in some studies that certain topically applied ocular hypotensive drugs (e.g., selective or nonselective beta-blockers, alpha agonists, carbonic anhydrase inhibitors, etc.) influence the ONH blood flow by direct ocular penetration and effect on the ONH blood vessels. However, drugs instilled in the conjunctival sac cannot readily reach the ONH in adequate concentration by direct penetration; hence, there is no scientific basis for the assumption that they have a direct action on the ONH circulation. Some of the drug may be absorbed into the systemic circulation and indirectly influence the ONH circulation; for example, it has been shown that persons using topical beta-blocker eye drops developed significant nocturnal arterial hypotension and nighttime bradycardia than those not using them.

Conclusions about Various Factors that Influence the ONH Circulation

The following crucial factors need to be considered when considering the pathogenesis of ischemic disorders of the ONH (including glaucomatous optic neuropathy) and their management.

i. Blood flow autoregulation plays a crucial role in the ONH circulation and many factors derange it. An ONH with deranged autoregulation is highly vulnerable to ischemic disorders.

ii. Vascular endothelial vasoactive agents play an important role in modulating the microvascular tone and blood flow in the ONH circulation. Production of these agents is impaired in many systemic and local conditions, and that would secondarily interfere with the ONH circulation.

iii. Nocturnal arterial hypotension is an important risk factor for the development of ONH ischemic disorders. The daytime-recorded BP gives no information whatever about the BP during sleep (Fig. 9).

iv. A rise of IOP during sleep and concurrent development of nocturnal arterial hypotension may together constitute an important hidden risk factor for ONH ischemia in vulnerable ONHs.

EVALUATION OF THE ONH CIRCULATION

Many methods have recently been put forward to evaluate ONH circulation and enthusiastic claims made. This is because of the increased recognition of the role of vascular insufficiency in the ONH in glaucomatous optic neuropathy and non-arteritic anterior ischemic optic neuropathy – two common visual disabling diseases. I have discussed the subject at length elsewhere. A critical review of the various advocated methods, including color Doppler imaging, transcranial Doppler, laser Doppler flowmetry, scanning laser Doppler flowmetry, magnetic resonance imaging, pulsatile ocular blood flow method, fluorescein fundus angiography, scanning laser fluorescein angiography, and temperature measurement, revealed that all these methods have limitations, and do not always give scientifically valid information on the actual ONH blood flow. Most of the recently advocated methods employ laser technology, e.g., laser Doppler flowmetry, scanning laser Doppler flowmetry and the laser speckle method. All of them suffer from the following fundamental flaw which invalidates their claims about the ONH blood flow: the laser beam in all of them is focused on the surface of the optic disc to measure the amount of blood flow in the ONH. As discussed above, the surface layer of the optic disc is supplied by the retinal circulation (Fig. 2), whereas glaucomatous optic neuropathy and non-arteritic anterior ischemic optic neuropathy are due to vascular insufficiency in the deeper ONH circulation, supplied by the posterior ciliary artery circulation (Fig. 2). Proponents of these laser methods have claimed that laser beam penetrates into the deeper tissues and measures the blood flow in the deeper layers of the ONH, but a recent controlled experimental study in monkeys showed that laser Doppler flowmetry predominantly measures the blood flow in the superficial layers of the ONH supplied by the retinal circulation (Fig. 2). The same applies to Heidelberg retinal flowmetry, and to the laser speckle method. Repeated claims of color Doppler imaging and pulsatile ocular blood flow methods measuring ONH blood flow are similarly invalid, for several reasons discussed in detail elsewhere.

The other common flaw has been to equate blood velocity with the amount of blood flow in the ONH; blood velocity does not provide information about the quantity of blood flow unless we know the size of the lumen of the vessels. That information is not provided by any of these methods. Therefore, none of the methods used so far provide scientifically valid information about the ONH blood flow and circulation, and one has to take the enthusiastic claims made by all these methods with marked skepticism.

Conclusions about Evaluation of the ONH Circulation

We do not have a single clinical method that gives scientifically valid information on the in vivo blood flow in the ONH - neither in health nor in disease.
OVERALL CONCLUSIONS

This brief review of the blood supply of the ONH and the factors that influence the blood flow in the ONH gives some idea of the great complexity of the subject. In ischemic disorders of the ONH, a large number of systemic and local factors acting in different combinations and to different extents may derange the circulation in the ONH. These risk factors may be:

1. **Predisposing risk factors** which make the ONH susceptible to ischemia, and
2. **Precipitating risk factors** which act as the final insult.\(^5,47,49,72\)

Available evidence strongly suggests that ONH ischemic disorders are multifactorial in nature.\(^2,47,49,72,73\) In such a multifactorial scenario, one set of risk factors may be responsible for ONH ischemia in one case and a very different set in another, and a particular risk factor may be present or critical in one case and not in another. Thus, each patient with ONH ischemic disorder may have a unique combination of systemic and local factors, which collectively produce ONH ischemic damage; no stereotyping is possible. Unfortunately, the widespread lack of understanding of the great complexity of ONH blood flow in health and disease, along with our inability to evaluate *in vivo* the ONH blood flow reliably, has caused much controversy on the subject of the role of vascular insufficiency in the ONH in glaucomatous optic neuropathy and non-arteritic anterior ischemic optic neuropathy.

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—Ralph Waldo Emerson