Ischemic optic neuropathy☆

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ABSTRACT

Ischemic optic neuropathy is one of the major causes of blindness or seriously impaired vision, yet there is disagreement as to its pathogenesis, clinical features and especially its management. This is because ischemic optic neuropathy is not one disease but a spectrum of several different types, each with its own etiology, pathogenesis, clinical features and management. They cannot be lumped together. Ischemic optic neuropathy is primarily of two types: anterior (AION) and posterior (PION), involving the optic nerve head (ONH) and the rest of the optic nerve respectively. Furthermore, both AION and PION have different subtypes. AION comprises arteritic (A-AION – due to giant cell arteritis) and, non-arteritic (NA-AION – due to causes other than giant cell arteritis); NA-AION can be further classified into classical NA-AION and incipient NA-AION. PION consists of arteritic (A-PION – due to giant cell arteritis), non-arteritic (NA-PION – due to causes other than giant cell arteritis), and surgical (a complication of several systemic surgical procedures). Thus, ischemic optic neuropathy consists of six distinct types of clinical entities. NA-AION is by far the most common type and one of the most prevalent and visually crippling diseases in the middle-aged and elderly. A-AION, though less common, is an ocular emergency and requires early diagnosis and immediate treatment with systemic high dose corticosteroids to prevent further visual loss, which is entirely preventable.

Controversy exists regarding the pathogenesis, clinical features and especially management of the various types of ischemic optic neuropathy because there are multiple misconceptions about its many fundamental aspects. Recently emerging information on the various factors that influence the optic nerve circulation, and also the various systemic and local risk factors which play important roles in the development of various types of ischemic optic neuropathy have given us a better understanding of their pathogeneses, clinical features and management. This knowledge should help us not only to manage them better but also to reduce their incidence. For example, clinically, the evidence that about 40% of NA-AION eyes experience spontaneous improvement in visual acuity and that systemic steroid therapy during early stages in both NA-AION and NA-PION has a significant beneficial effect for visual outcome are encouraging developments. This review discusses the current concepts on various issues related to various types of ischemic optic neuropathy.

Contents

1. Introduction

Ischemic optic neuropathy constitutes one of the major causes of blindness or seriously impaired vision among the middle-aged and elderly population, although no age is immune. Its pathogenesis, clinical features and management have been subjects of a good deal of controversy and confusion. I have conducted basic, experimental and clinical research on the blood supply of the optic nerve and on various aspects of ischemic optic neuropathy since 1955. This review is based on the cumulative information drawn from those studies, as well as from a PubMed search of the literature on the subject.

2. Terminology

Before 1974, this condition was described under different eponyms, including optic neuritis, arteriosclerotic papillitis, senile papillopathy, papillary apoplexy, vascular pseudo-papillitis, optico-malacia, ischemic neuritis of papilla, ischemic papillopathy and ischemic optic neuritis and so on (Hayreh, 1975a). Since studies have shown that it is an acute ischemic disorder of the optic nerve, the proper terminology for this disease is "ischemic optic neuropathy". Based on the blood supply pattern of the optic nerve, and my clinical and experimental studies, in 1974 I defined ischemic optic neuropathy into the following two distinct clinical entities.

2.1. Anterior ischemic optic neuropathy (AION)

This is due to ischemia of the anterior part of the optic nerve, which is supplied by the posterior ciliary artery (PCA) circulation (Hayreh, 1969, 1995, 2001b) (Fig. 1A). In view of that I named it "anterior ischemic optic neuropathy" (Hayreh, 1974b).

2.2. Posterior ischemic optic neuropathy (PION)

I first described this clinical entity in 1981 (Hayreh, 1981b); it is due to ischemia of a segment of the posterior part of the optic nerve, which is supplied by multiple sources but not the PCA (Figs. 1B and 2).

Of the two types, AION is far more common than PION. Pathogenetically and clinically AION and PION are quite distinct clinical entities; thus, the common practice of calling AION simply "ischemic optic neuropathy" is incorrect, and "ischemic optic neuritis" is worse still, since there is no evidence of inflammation.

From the basic scientific facts about the disease process, one can logically deduce its pathogenesis, clinical features and management. The basic sciences are the foundation of Medicine. To comprehend the scientific basis of the pathogeneses, various clinical features and management of AION and PION, the first essential is to have a good understanding of the various basic scientific issues involved. Since this is an ischemic disorder of the optic nerve, the
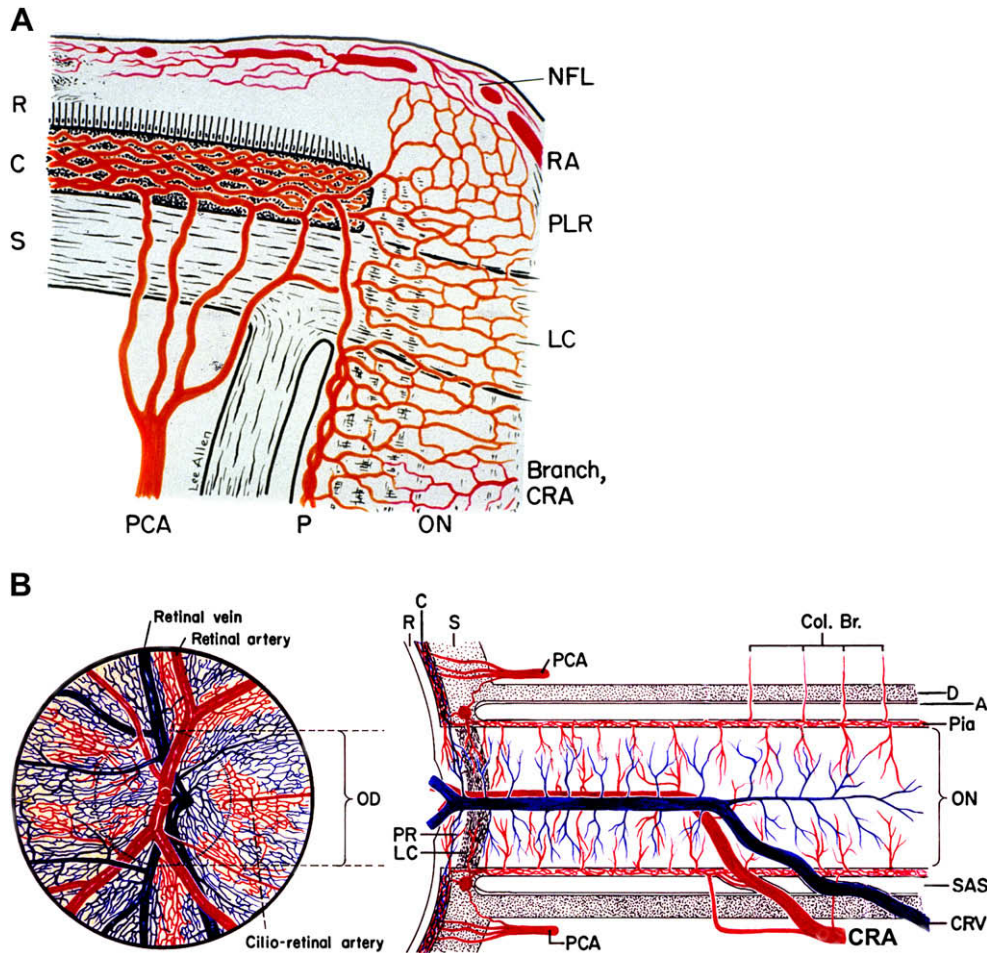
Fig. 1. Schematic representation of blood supply of: (**A**) the optic nerve head and (**B**) the optic nerve (**B** modified from Hayreh, S.S. (1974) Trans. Am. Acad. Ophthalmol. Otolaryngol. 78, OP240–OP254. **A** reproduced from Hayreh, 1978a). *Abbreviations:* A = arachnoid; Ant. Sup. Hyp. Art. = anterior superior hypophyseal artery; C = choroid; CAR and CRA = central retinal artery; Col. Br. = collateral branches; CRV = central retinal vein; CZ = circle of Zinn and Haller; D = dura; ICA = internal carotid artery; LC = lamina cribrosa; LPCA = lateral posterior ciliary artery; Med. Mus. = medial muscular artery; MPCA = medial posterior ciliary artery; NFL = surface nerve fiber layer of the disc; OA = ophthalmic artery; OD = optic disc; ON = optic nerve; P = pia; PCA = posterior ciliary artery; PR and PLR = prelaminar region; R = retina; RA = retinal arteriole; Rec. Br. CZ = recurrent pial branches from peripapillary choroid/CZ; S = sclera; SAS = subarachnoid space.

first basic issue is the blood supply of the optic nerve and the role of various factors in the production of acute optic nerve ischemia.

3. Blood supply of the optic nerve

Based on its blood supply pattern, the optic nerve can be divided into two distinct regions: (a) anterior (also called optic nerve head – ONH); and (b) posterior.

3.1. Anterior part of the optic nerve (ONH)

Blood supply of this part is described in detail elsewhere (Hayreh, 1969, 1995, 2001b). Following is a brief summary.

3.1.1. Arterial supply (Fig. 1A)
Anatomically ONH consists of, from front to back: (i) surface nerve fiber layer; (ii) prelaminar region; (iii) lamina cribrosa region; and (iv) retrolaminar region (Hayreh and Vrabec, 1966; Hayreh, 1972) (Fig. 1A).

3.1.1.1. The surface nerve fiber layer. This is mostly supplied by the retinal arterioles. In some cases, its temporal region may instead be supplied by the PCA circulation from the deeper prelaminar region. The cilioretinal artery (rarely a tiny cilio-papillary artery), when present, usually supplies the corresponding sector of the surface layer.

3.1.1.2. The prelaminar region. This is situated between the surface nerve fiber layer and the lamina cribrosa. It is supplied by fine centripetal branches from the peripapillary choroid. The central retinal artery gives no branches in this region. The blood supply in this region is sectoral in nature, similar to the overall segmental distribution of the PCA circulation (Hayreh, 1975b, 2004a).

3.1.1.3. The lamina cribrosa region. This is supplied by centripetal branches from the short PCAs either directly or by the so-called arterial circle of Zinn and Haller, when that is present. The central retinal artery gives off no branches in this region. In the lamina cribrosa, the blood vessels, 10–20 μ in diameter, lie in the fibrous septa and form a dense capillary plexus that makes this part of the ONH a highly vascular structure (Levitzky and Henkind, 1969).

3.1.1.4. The retrolaminar region. This lies immediately behind the lamina cribrosa. This part of the ONH may have a dual source of blood supply (Figs. 1A,B and 2).

3.1.1.4.1. The peripheral centripetal vascular system. This is always present and forms the major source of supply here. It is formed by recurrent pial branches arising from the peripapillary choroid and circle of Zinn and Haller (when present) or the short PCAs instead. In addition, pial branches from the central retinal artery and other orbital arteries also supply this part (Hayreh, 1958;
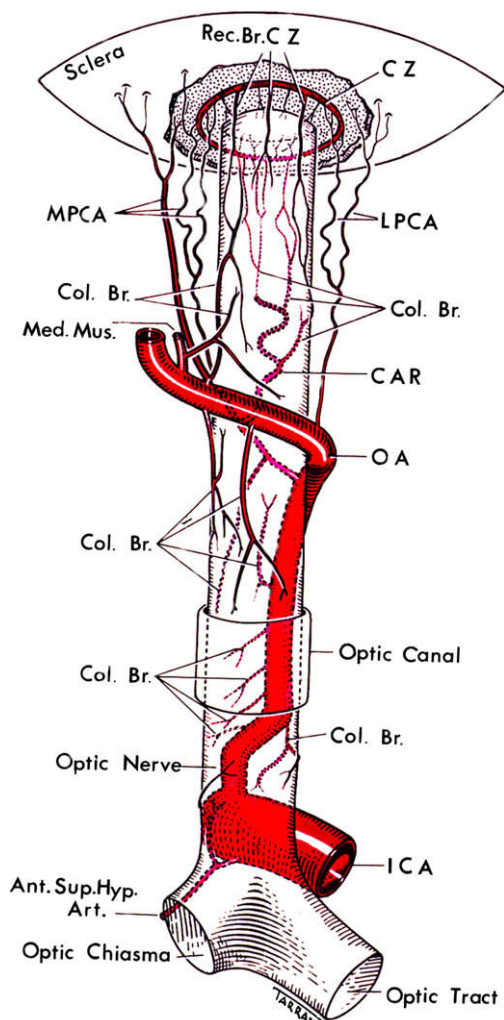
Fig. 2. Diagrammatic representation of blood supply of the various parts of the optic nerve, and location of the circle of Haller and Zinn (CZ), as seen from above. For abbreviations see Fig. 1. (Reproduced from Hayreh, 1963b).

Singh and Dass, 1960b). The pial vessels give off centripetal branches, running in the septa of the nerve.

3.1.1.4.2. The axial centrifugal vascular system. This is not present in all eyes. When present, it is formed by branches arising from the intraneural part of the central retinal artery (Hayreh, 1958; Singh and Dass, 1960b)

Thus, the main source of blood supply to the ONH is the PCA circulation via the peripapillary choroid and the short PCAs (or the circle of Zinn and Haller). The blood supply in the ONH has a sectoral distribution, which helps to explain the segmental visual loss in ONH ischemic disorders.

3.1.2. Venous drainage (Fig. 1B)

This is essentially via the central retinal vein except that the prelaminar region also drains into the peripapillary choroidal veins (Hayreh, 1969). This latter communication assumes importance in developing retinociliary collaterals (misnamed optociliary shunts) in the event of central retinal vein occlusion behind the lamina cribrosa.

3.2. Posterior part of the optic nerve (Figs. 1B and 2)

For purposes of description of the blood supply, the posterior part of the optic nerve can be divided into intraorbital, intracanalicular and intracranial parts (Hayreh, 1963a).

3.2.1. Arterial supply

3.2.1.1. Intraorbital part. This is further subdivided by point of entry of the central retinal artery in the optic nerve into: (a) anterior; and (b) posterior segments (Figs. 1B and 2) (Singh and Dass, 1960b; Hayreh, 1963a,b).

3.2.1.1.1. Anterior segment. This is between the ONH and the site of entry of the central retinal artery into the nerve (Fig. 1B). It has two vascular systems for its supply.

3.2.1.1.1.1. Peripheral centripetal vascular system. This is present in all cases and is formed by pial vascular plexus, supplied by multiple pial branches originating from the peripapillary choroid, circle of Zinn and Haller, central retinal artery, ophthalmic artery and other orbital arteries (Figs. 1B and 2).

3.2.1.1.1.2. Axial centrifugal vascular system. This is present in 75% of the nerves and supplied by one to eight intraneural branches of the central retinal artery (Fig. 1B).

3.2.1.1.2. Posterior segment. This is primarily supplied by the peripheral centripetal vascular system formed by the pial vascular plexus, supplied by multiple small collateral arteries usually arising directly from the ophthalmic artery and less often from other orbital arteries (Figs. 1B and 2) (Hayreh, 1963a). In about 10% of optic nerves there may be an axial centrifugal vascular system extending backward for a variable distance, formed by intraneural branches of the central retinal artery (Fig. 3) (Hayreh, 1958).

3.2.1.2. Intracanalicular part. This has only the peripheral centripetal system, supplied almost entirely by fine collateral branches from the ophthalmic artery lying inferior to the optic nerve (Fig. 2) (Hayreh, 1963a,b).

3.2.1.3. Intracranial part. This once again has only a pial vascular plexus, supplied by a variable number of fine branches coming from various surrounding arteries, including the anterior superior hypophyseal, anterior cerebral, anterior communicating and ophthalmic arteries (Fig. 2) (Hayreh, 1963a,b).

3.2.2. Venous drainage (Fig. 1B)

This is by the central retinal vein and also many other small venous tributaries draining into the various orbital veins.

3.3. Interindividual variations in the blood supply of the optic nerve

There exists a general impression that the pattern of blood supply of the optic nerve is almost identical in all eyes, and that all ischemic lesions are explainable from one standard vascular pattern. This is a fundamental error, which is responsible for much confusion. This is particularly so for the blood supply of the ONH, which shows marked interindividual variations, as discussed at length elsewhere (Hayreh, 1985, 1995, 2001b). Briefly, the following factors are responsible for the interindividual variations in the blood supply of the ONH.

3.3.1. Variations in the anatomical pattern

This has wide variations, so much so that in Hayreh's (1958, 1962; Singh and Dass, 1960a,b) anatomical studies no two specimens had identical patterns, not even the two eyes of the same individual. So the anatomical vascular pattern of the optic nerve is far from standard in all humans.

3.3.2. Variations in the pattern of PCA circulation

These are produced by several factors.

3.3.2.1. Variations in number of PCAs supplying an eye. There may be one to five PCAs, usually two to three (Hayreh, 1962, 1995, 2001b).
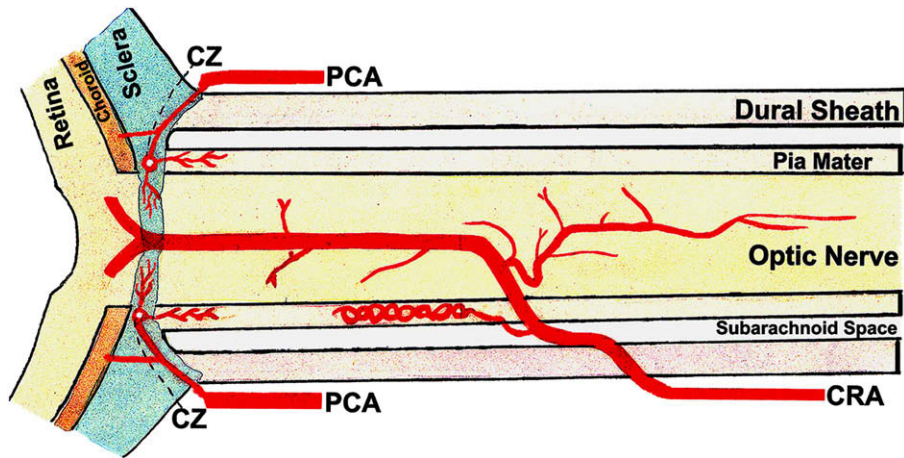
Fig. 3. Diagram (based on camera lucida drawings) showing one of the intraneural branches of the central retinal artery running backward in the axial part of the optic nerve posterior to the central retinal artery. From one of the specimens in my anatomical study on the central retinal artery in humans. For abbreviations see Fig. 1. (Reproduced from Hayreh, 1958).

3.3.2.2. Variations in the area supplied by various PCAs. In humans, this shows marked interindividual variation (Hayreh, 1990b, 2004a). PCAs and their branches have a segmental distribution *in vivo*, in the choroid as well as in the ONH (Hayreh, 1975b, 1985, 1990b, 2004a). Therefore, with the interindividual variation in number and distribution by the various PCAs, we can get an extremely variable pattern of distribution by the PCAs in both the choroid and the ONH – a key fact to be borne in mind in any consideration of ischemic disorders of the ONH, since PCAs are its main source of blood supply. For example, Fig. 4 shows three such variations in the supply by the medial and lateral PCAs in the choroid and the ONH; the part of the ONH involved depends upon the area supplied by the occluded PCA.
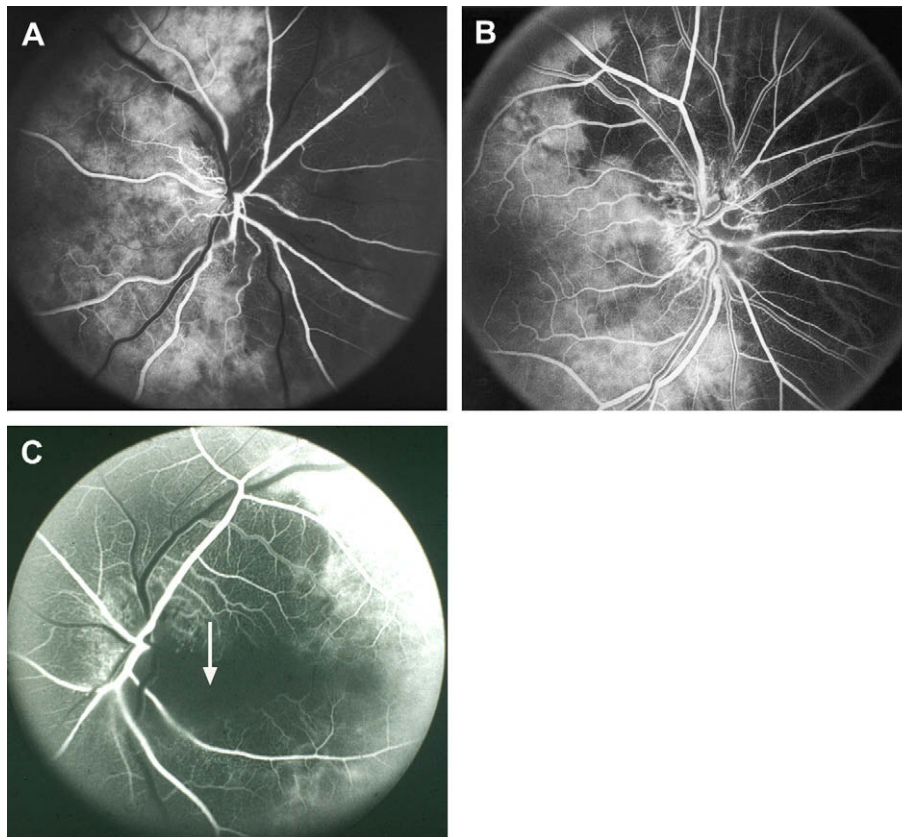
Fig. 4. Fluorescein fundus angiograms of three eyes showing areas of supply by the occluded PCA and the patent PCA. (**A**) Right eye with NA-AION (negative temporal artery biopsy for giant cell arteritis), showing normal filling of the area supplied by the lateral PCA (including the temporal half of optic disc) but no filling of the area supplied by the medial PCA (including the nasal half of optic disc). (Reproduced from Hayreh, 1985). (**B**) Right eye with A-AION, showing normal filling of the area supplied by the lateral PCA (including the temporal ¼ of the optic disc) but no filling of the area supplied by the medial PCA (including the nasal $\frac{3}{4}$ of the disc). (Reproduced from Hayreh, 1978b). (**C**) Left eye with A-AION associated with cilioretinal artery occlusion, showing normal filling of the area supplied by the lateral PCA, but no filling of the choroid and entire optic disc supplied by the medial PCA or of the cilioretinal artery (arrow). (Reproduced from Hayreh, 1978b).

3.3.2.3. Variation in location of watershed zones between the PCAs in relation to the ONH. This again plays an important role in ischemic disorders of the ONH, because the location of the watershed zone determines the vulnerability of the corresponding part of the ONH to ischemia (Hayreh, 1985, 1990b). In the event of a fall of perfusion pressure in the PCAs or their branches, the part of the ONH located in the watershed zone becomes vulnerable to ischemia. For example, Fig. 5 shows four variations in the location of watershed zone between the medial and lateral PCAs; the part of the ONH involved depends upon the relationship of ONH to the location of the watershed zone.

3.3.2.4. Variation in mean blood pressure in various PCAs as well as short PCAs. This may occur in health as well as in disease (Hayreh, 1985). In the event of a fall of perfusion pressure, the vascular bed supplied by one artery may be affected earlier and more than the others.

4. Factors influencing the blood flow in the optic nerve head

These factors are critical to understanding the pathogenesis of ischemic disorders of the ONH. This subject is discussed at length elsewhere (Hayreh, 2001c). Following is a brief summary of that.

4.1. Blood flow formula

The blood flow in the ONH is calculated by the following formula:

$$\text{Blood flow} = \frac{\text{Perfusion pressure}}{\text{Resistance to flow}}$$

Perfusion pressure = mean BP minus intraocular pressure (IOP).
Mean BP = diastolic BP +1/3 (systolic minus diastolic BP).

Thus the blood flow in the ONH depends upon: (i) resistance to blood flow; (ii) BP; and (iii) IOP.

4.1.1. Resistance to blood flow

A large number of factors can influence resistance to blood flow in the ONH. These include: (a) efficiency of autoregulation of the ONH blood flow; (b) vascular changes in the arteries and arterioles supplying the ONH circulation; and (c) rheological properties of the blood.

4.1.1.1. Autoregulation of blood flow in the ONH. This plays an important role (discussed at length elsewhere (Hayreh, 2001c)). Briefly, the goal of autoregulation in a tissue is to maintain relatively constant blood flow, capillary pressure and nutrient supply in spite of changes in perfusion pressure. Autoregulation of blood flow is due to alteration in the resistance to blood flow and that in turn is due to changes in the tone of the blood vessels. 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
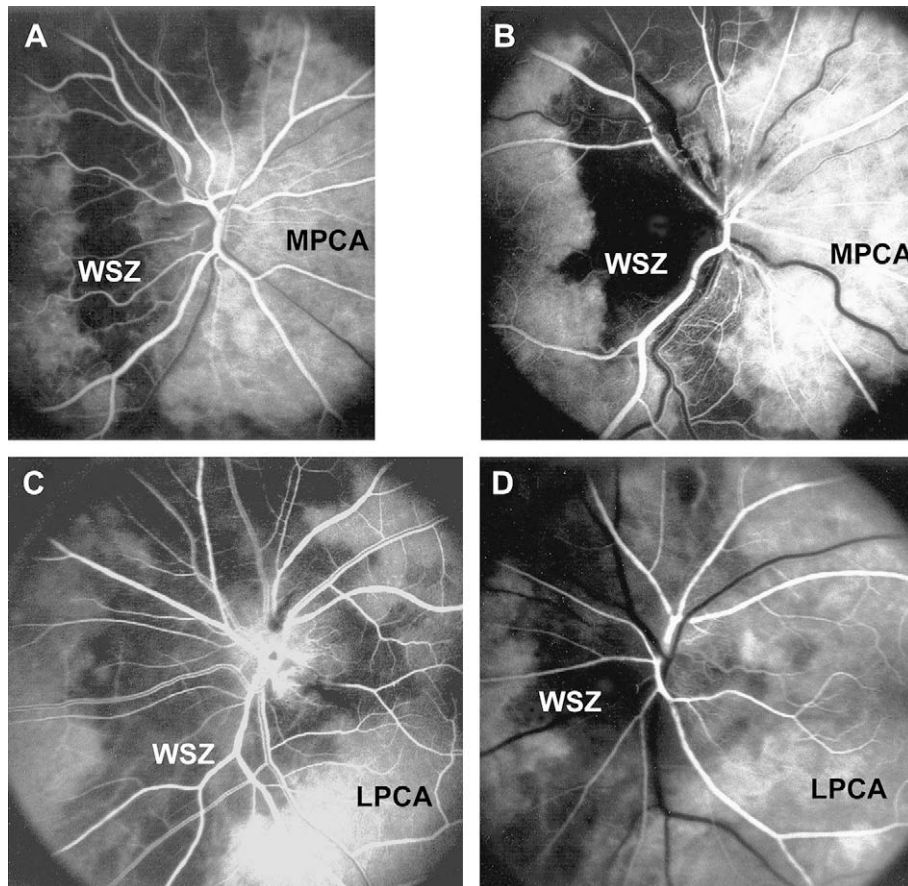
Fig. 5. Fluorescein fundus angiograms of four eyes with AION showing different locations of the watershed zone (vertical dark bands) in relation to the optic disc. (**A**) Right eye with the watershed zone lying temporal to the optic disc. (**B**) Right eye with the watershed zone passing through the 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. (Reproduced from Hayreh, 1985).

Fig. 6. A diagrammatic representation of blood flow autoregulation range at different perfusion pressures in normal persons. Absent and present denote absence or presence of the autoregulation.

hypertension. Recent studies have shown that pericytes in the capillaries may also play a role in regulation of the blood flow autoregulation by virtue of the presence of contractile proteins actin and myosin. Since there is a limit to how far the terminal arterioles or capillaries can constrict or dilate, the autoregulation operates only within a certain critical range of perfusion pressure, and breaks down when the perfusion pressure goes below or above this critical range (Fig. 6).

The exact mechanism of blood flow autoregulation is still not known, and various hypotheses have been put forward (Hayreh, 2001c). Briefly, there are three hypotheses. (i) Metabolic hypothesis: according to this, local arteriolar smooth muscle tone is regulated by local concentration of metabolic products, pO_2 and pCO_2, and they play a role in maintaining autoregulation. (ii) Myogenic hypothesis: according to this, the rise of intra-vascular pressure causes vasoconstriction. (iii) Neurogenic hypothesis: we do not have much evidence of this in the ONH, since vessels in the retina and ONH have no autonomic nerve supply but both still have autoregulation. The choroid, by contrast, is richly supplied by the autonomic nerves and yet has no appreciable autoregulation.

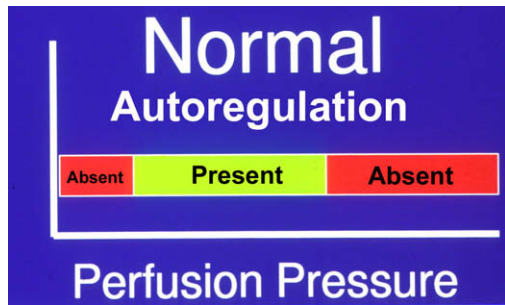*4.1.1.1.1. What is the range of perfusion pressure over which ONH autoregulation operates?.* Autoregulation operates only over a critical range of perfusion pressure, so that with a rise or fall of perfusion pressure beyond the critical range, the autoregulation becomes ineffective and breaks down (Fig. 6). In normal monkeys, autoregulation in the ONH has been reported to be normal at a perfusion pressure of $\geq$30 mmHg by Bill and co-workers (Geijer and Bill, 1979; Sperber and Bill, 1985) and >50 mmHg by Ernest (1976), but it definitely breaks down below 30 mmHg (Bill and Sperber, 1987). In old, atherosclerotic rhesus monkeys, ONH autoregulation was already defective at 30–35 mmHg perfusion

pressure (Hayreh et al., 1994a). In the human, the level of perfusion pressure below which the autoregulation breaks down may vary from person to person. This is because autoregulation in the ONH may be deranged by many factors (discussed in detail elsewhere (Hayreh, 2001c)), including systemic and local causes, e.g., the aging process, arterial hypertension, diabetes mellitus, arteriosclerosis, atherosclerosis, and hypercholesterolemia (Haefliger et al., 1994; Hayreh et al., 1994a). When marked arterial hypotension from any cause results in fall of perfusion pressure below the critical autoregulation range (Fig. 6), that also results in a breakdown of autoregulation. In addition to these known factors, there may perhaps be still other unknown factors. When there is a breakdown of autoregulation, the blood flow is directly proportional to the perfusion pressure. Thus, it is essential to remember that autoregulation does not protect the ONH blood flow at all times. Unfortunately, we do not have a clinical method to evaluate autoregulation in humans.

4.1.1.2. Role of blood flow autoregulation in ischemic disorders of the ONH. Autoregulation plays an important role in ONH ischemic disorders. Since the autoregulation is effective over only a narrow critical range normally (Fig. 6), any change in the perfusion pressure above or below that range makes the ONH vulnerable to ischemia. The mere existence of autoregulation does not necessarily always protect the ONH.

4.1.2. Arterial blood pressure

This is an important determinant of blood flow in the ONH. Both arterial hypertension and hypotension can influence the ONH blood flow in a number of ways. Arterial hypertension can derange ONH blood supply by increased vascular resistance in the terminal arterioles, secondary hypertensive vascular changes in ONH vessels, and by deranging blood flow autoregulation. In an ONH, a fall of BP below a critical level of autoregulation would decrease its blood flow. Fall of BP in the ONH may be due to systemic or local hypotension.

4.1.3. Intraocular pressure

ONH blood flow depends upon the perfusion pressure, which is equal to mean BP minus IOP. Thus, there is an inverse relationship between IOP and perfusion pressure in the ONH.

4.1.4. Conclusion

This, then, gives some idea of the great complexity of the blood supply and blood flow in the ONH. In ischemic disorders of the ONH, a whole host of systemic and local factors acting in different
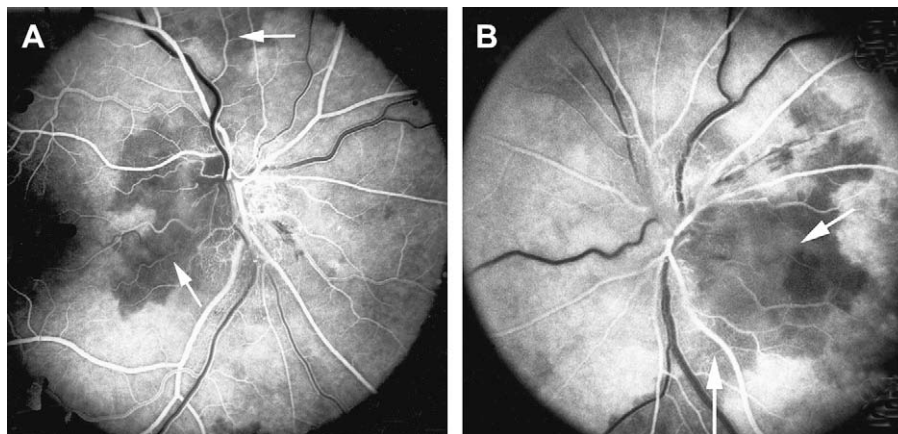

Fig. 7. Fluorescein fundus angiogram of two eyes with NA-AION showing non-filling of temporal part of the peripapillary choroid (arrow) and adjacent optic disc and the choroidal watershed zone (arrow). [Reproduced from (**A**) Hayreh, 1985 and (**B**) Hayreh, 1996].

combinations and to different extents may derange the circulation in the ONH, with some making the ONH susceptible to ischemia while others act as the final insult in one case and vice versa in another. Moreover, one set of factors may be responsible for ONH ischemia in one case and a totally different set in another, and so on. In such a scenario, a particular factor may be present in one case and not in another. Thus ONH ischemic disorders are multifactorial in nature, particularly in AION, according to the available evidence (Hayreh et al., 1994b,c). Each patient with non-arteritic AION or other ONH ischemic disorders may have a unique combination of systemic and local factors which together produce ONH ischemic damage (Hayreh, 1996). It is the lack of awareness of this complexity of ONH blood flow which is responsible for most of the controversy and confusion about AION.

5. Ischemic optic neuropathy

5.1. Classification

As discussed above, based on the two very distinct patterns of the blood supply patterns of the ONH and rest of the optic nerve, ischemic optic neuropathy is of two distinct types (Hayreh, 1974c).

5.1.1. Anterior ischemic optic neuropathy (AION)
This is due to ischemia of the ONH. Etiologically and pathogenetically, AION is of two types (Hayreh, 1974c, 1978b, 1981c, 1990a).

5.1.1.1. Arteritic AION (A-AION). This is due to giant cell arteritis (GCA).

5.1.1.2. Non-arteritic AION (NA-AION). This type is not due to GCA.

5.1.2. Posterior ischemic optic neuropathy (PION) (Hayreh, 1981b, 2004b)
This is due to involvement of the rest of the optic nerve.

5.2. Non-arteritic anterior ischemic optic neuropathy (NA-AION)

This is the most common type of ischemic optic neuropathy, and has attracted the most controversy as to its pathogenesis and management.

5.2.1. Pathogenesis
This is discussed at length elsewhere (Hayreh, 1996). Following is a brief account:

NA-AION is due to acute ischemia of the ONH (Hayreh, 1974b, 1981c, 1985), whose main source of blood supply is from the PCA circulation (Fig. 1A). Therefore, NA-AION represents an ischemic disorder of PCA circulation in the ONH. Marked interindividual variations in blood supply of the ONH (see above) and its blood flow patterns profoundly influence the pathogenesis and clinical features of NA-AION. This entire subject is very controversial and requires a detailed discussion to place the various relevant issues in proper perspective.

Etiologically and pathogenetically NA-AION is of two types.

5.2.1.1. Due to transient non-perfusion or hypoperfusion of the ONH circulation. This is by far the commonest cause of NA-AION (Hayreh, 1996; Hayreh et al., 1994c, 1997b, 1999). There is almost a universally held belief among ophthalmologists and neurologists that NA-AION has a pathogenesis like that of a stroke which is a thromboembolic disorder; however, in the vast majority of NA-AION cases there is no evidence of that, as indicated by the following evidence.

(i) First and foremost, if NA-AION were a thromboembolic disorder, like A-AION, fluorescein fundus angiography during the early stages of onset of visual loss must almost invariably show evidence of complete occlusion of the vessels supplying the ONH (as is the case in A-AION – see below); however, no such occlusion is seen in NA-AION. Fluorescein fundus angiography soon after the onset of NA-AION shows only a delayed and slow filling of the peripapillary choroid and/or choroidal watershed zones, but no permanent occlusion (Figs. 5A,B,D and 7) which provides a definite proof that NA-AION is not a thromboembolic occlusive disorder.

(ii) The severity of ONH ischemic damage depends upon the severity and the duration of the ONH ischemia; the latter determines the extent of recovery of visual function following the acute episode. In NA-AION, because there is only transient non-perfusion or hypoperfusion the ONH circulation, there is usually much less severe and less extensive ONH damage than in A-AION, in which there is thrombotic occlusion of the PCA. Two large studies (Ischemic Optic Neuropathy Decompression Trial Research Group, 1995; Hayreh and Zimmerman, 2008a) have shown that in NA-AION 41% of the eyes show spontaneous visual improvement. In sharp contrast to that, in A-AION no such visual improvement is seen (Hayreh and Zimmerman, 2003b).

(iii) In NA-AION patients, compared to age-matched controls, transcranial Doppler did not reveal an increased incidence of embolic events, which further confirms that NA-AION is not a thromboembolic disorder (Kosmorsky et al., 1998).

Thus, all the available evidence indicates that NA-AION is not a thromboembolic disorder. Naturally the question arises: what is the mechanism of transient non-perfusion or hypoperfusion of the ONH circulation in NA-AION? It can be caused by a variety of factors. Available evidence indicates that in the vast majority of cases it is a transient fall of blood pressure, most commonly during sleep (nocturnal arterial hypotension – see below) or a nap during the day (Hayreh et al., 1994c, 1999), and more rarely ocular ischemia, severe internal carotid artery and/or ophthalmic artery stenosis or occlusion during sleep (Mizener et al., 1997). Any kind of shock can also cause a transient fall of blood pressure. A sharp rise in the IOP to high levels (e.g., in neovascular glaucoma associated with ocular ischemia, or angle closure glaucoma) can also cause a transient fall in perfusion pressure (perfusion pressure is equal to mean blood pressure minus IOP).

A transient fall of perfusion pressure in the ONH vessels results in transient non-perfusion or hypoperfusion of those vessels. As discussed above, a fall in perfusion pressure in the capillaries of the ONH below the critical autoregulatory range level (Fig. 6), in susceptible persons (see below), results in ischemia of the ONH and development of NA-AION. The severity of ONH ischemia may vary from mild to marked, depending upon the severity and the duration of the transient ischemia and other factors influencing the blood flow in the ONH (see above).

5.2.1.2. Due to embolic lesions of the arteries/arterioles feeding the ONH. This is only an occasional cause of NA-AION. Multiple emboli in the vessels of the anterior part of the optic nerve have been demonstrated histopathologically in AION (Lieberman et al., 1978). This has also been shown on fluorescein fundus angiography (Fig. 4A) (Hayreh, 1985). Compared to the hypotensive type of NA-AION, the extent of ONH damage in this type is usually massive, severe, and permanent (similar to that in A-AION – see below), depending upon the size of the artery involved and the area of the nerve supplied by the occluded artery.

5.2.2. Risk factors for development of NA-AION
All the available evidence indicates that NA-AION is multifactorial in nature. The risk factors fall into two main categories.

5.2.2.1. Predisposing risk factors. These may be systemic or local in the eye and/or ONH, and they may make the ONH susceptible to ischemic disorders but do not necessarily produce NA-AION on their own.

5.2.2.1.1. Systemic risk factors. Various studies have shown a significantly high prevalence of arterial hypertension, nocturnal arterial hypotension, diabetes mellitus, ischemic heart disease, hyperlipidemia, atherosclerosis and arteriosclerosis in NA-AION patients compared to the general population (Repka et al., 1983; Guyer et al., 1985; Hayreh et al., 1994b; Hayreh, 1996; Jacobson et al., 1997; Hayreh and Zimmerman, 2008c). Other associated systemic diseases have also been reported, including sleep apnea (Hayreh, 1996; Mojon et al., 2002; Palombi et al., 2006; Li et al., 2007), arterial hypotension due to a variety of causes including, shock, cardiopulmonary bypass surgery and hemodialysis, massive or recurrent hemorrhages (Hayreh, 1987) and malignant arterial hypertension (Hayreh et al., 1986a). The possibility that in an occasional patient embolism from thrombophilic factors may cause NA-AION cannot be ruled out (Hayreh, 2008d). Similarly, other rare causes include, migraine, defective cardiovascular autoregulation, "Type A personality" (Hayreh, 1996), and carotid dissection (Biousse et al., 1998). In addition, the literature is full of anecdotal case reports of the association of "anterior ischemic optic neuropathy" with a large variety of systemic diseases and causes, but it is not possible to establish a cause-and-effect relationship in all of them. However, these rare diseases have no role in the vast majority of NA-AION cases, since it is primarily a hypotensive disorder.

5.2.2.1.2. Ocular and ONH risk factors. A significant association of NA-AION has been seen with a number of ocular and ONH conditions. These include absent or small cup in the optic disc (Beck et al., 1987; Hayreh and Zimmerman, 2008d), angle closure glaucoma or other causes of markedly raised IOP (Hayreh, 1980), marked optic disc edema due to any cause (Hayreh, 1977b), location of the watershed zone of the PCAs in relation to the optic disc (Hayreh, 1990b), and vascular disorders in the nutrient vessels of the ONH (Hayreh, 1995), optic disc drusen and cataract extraction (Hayreh, 1980). There are a few reports of delayed development of NA-AION in the fellow eyes long after cataract extraction in one eye (Nguyen et al., 2006; Lam et al., 2007), implying that cataract extraction *per se* is a risk factor; there is no evidence in support of that. This is because a person who has the required risk factors, is at risk of developing NA-AION irrespective of whether he/she has cataract extraction or not – the fact that he/she developed NA-AION after cataract extraction in the first eye indicates the presence of those predisposing risk factors in him/her. Optic disc related visual field defects detected after vitrectomy (Taban et al., 2007) are most probably due to development of NA-AION in those eyes during vitrectomy, due to intra- and/or postoperative raised IOP, along with other associated systemic risk factors mentioned above.

5.2.2.1.2.1. The role of an absent or small cup in the pathogenesis of development of NA-AION. Since 1974, several studies have shown that in eyes with NA-AION there is a significantly higher prevalence of absent or small cup than in the general population (Hayreh, 1974a; Hayreh and Zimmerman, 2008d). This has resulted in a misconception in the ophthalmic community that a small or absent cup is actually the primary factor in the development of the disease; this has resulted in terms like "disc at risk". The role of an absent or small cup in the pathogenesis of development of NA-AION is discussed in detail elsewhere (Beck et al., 1987; Hayreh and Zimmerman, 2008d). Briefly, in the multifactorial scenario of the pathogenesis of NA-AION, one has to consider the role of the following two factors relevant to cup/disc ratio. (a) Absent or small cup is associated with a small scleral canal and small opening in the Bruch's membrane, resulting in crowding of the optic nerve fibers as they pass through the restricted space in the optic disc and lamina cribrosa. (b) Ischemia or hypoxia of the axons in the ONH causes axoplasmic flow stasis, which in turn results in swollen axons (Hayreh, 1977a). Axoplasmic flow stasis causes swelling of the axons and that is responsible for optic disc edema in ischemic optic neuropathy (McLeod et al., 1980). If the optic disc has a cup, the swollen axons can expand into that without compressing any other tissues in the optic disc. But when there is no cup or only a small cup, the swollen axons are crowded in a restricted space in the optic disc, and they can expand only by compressing the surrounding tissues. The tissues that are most vulnerable to compression here are capillaries and other fine vessels lying among the nerve fibers. Thus, swollen axons in restricted space within the optic disc produce secondary vascular changes (Hayreh, 1977a). It has been shown that asymptomatic optic disc edema is the earliest sign of NA-AION (Hayreh, 1981a; Hayreh and Zimmerman, 2007a). It has also been demonstrated that nocturnal arterial hypotension precipitates the development of NA-AION (Hayreh et al., 1997b). Thus, the available evidence indicates that the sequence of events in the development of NA-AION are as follows: subclinical ischemia (hypoxia) of the optic nerve head → axoplasmic flow stasis in the optic nerve fibers → axonal swelling → asymptomatic optic disc edema (incipient NA-AION (Hayreh, 1981a; Hayreh and Zimmerman, 2007a)) → compression of the intervening capillaries by swollen axons in a crowded disc → setting up a vicious cycle: the greater the compression of capillaries, the greater the blood flow compromise, the greater the axoplasmic flow stasis and the more the axonal swelling. Since compression of the optic disc capillaries compromises their blood flow, a fall of blood pressure must further derange their blood flow. Therefore, in this situation, a fall of perfusion pressure in the optic disc capillaries due to nocturnal arterial hypotension results in marked ischemia and that precipitates visual loss (symptomatic NA-AION), which is usually discovered on waking up in the morning (Hayreh et al., 1997b).

From this sequence of events, it is evident that in the multifactorial scenario of pathogenesis of NA-AION, contrary to the prevalent impression, an absent or small cup is simply a secondary contributing factor, ONCE the process of NA-AION has started, and NOT a primary factor (Beck et al., 1987; Hayreh and Zimmerman, 2007a,b).

5.2.2.2. Precipitating risk factor(s). In a person with a predisposing risk factor already present, these risk factors act as the final insult ("last straw"), resulting in ischemia of the ONH and NA-AION. Nocturnal arterial hypotension is the most important factor in this category (Hayreh et al., 1994c, 1997b, 1999). Studies have shown that patients with NA-AION and often also those with A-AION typically complain of discovering visual loss on waking in the morning. In NA-AION, 73% gave a definite history of discovering the visual loss on waking up in the morning or from a nap, or first opportunity in the day to use vision critically (Hayreh et al., 1997b). The incidence may actually be much higher than 73% because many others who became aware of visual loss later on in the day could not be certain when it had occurred. Hayreh et al.'s (1994c, 1999) 24-h ambulatory blood pressure monitoring has shown development of marked nocturnal arterial hypotension in such patients. For example, the 24-h ambulatory blood pressure monitoring pressure graph in Fig. 8 shows a steep drop in blood pressure on falling asleep at night and recovery to normal on waking in the morning. Studies have also shown that arterial hypertensives on oral hypotensive therapy have a significant ($p = 0.004$) association between progressive visual field deterioration in NA-AION and nocturnal hypotension (Hayreh et al., 1994c, 1999). The fall of blood pressure during sleep is a physiological phenomenon, but it is influenced by many factors, including the various arterial hypotensive drugs taken for arterial hypertension or other cardiovascular disorders, particularly the number and amount of drugs taken and the time of day they are
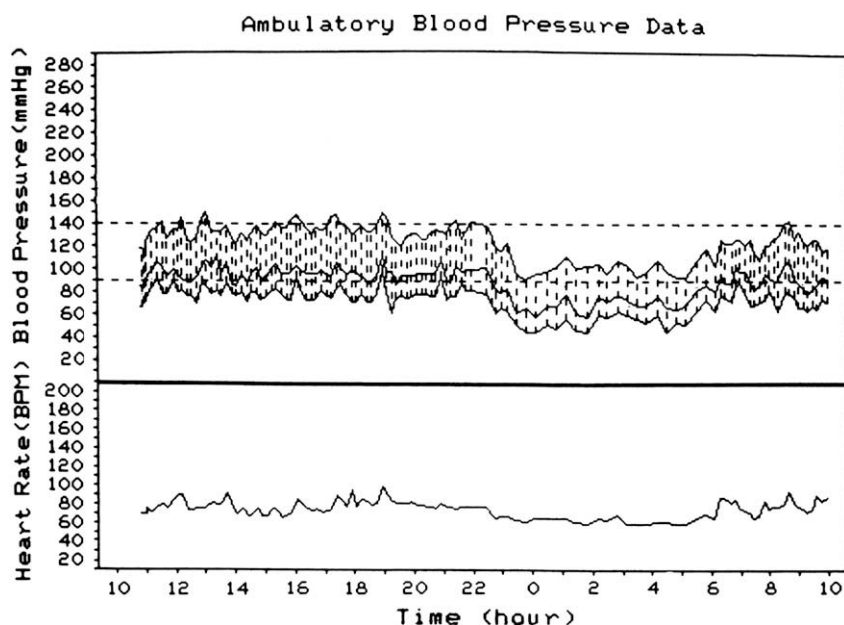
Fig. 8. Ambulatory BP and heart rate monitoring records (based on individual readings) over a 24-h period, starting from about 11 a.m., in a 58-year old woman with bilateral NA-AION, and on no medication. The BP is perfectly normal during the waking hours but there is marked nocturnal arterial hypotension during sleep. (Reproduced from Hayreh et al., 1999).

taken. When these drugs were taken at bedtime, they produced a far more marked degree of nocturnal hypotension than when taken in the morning, because they aggravate the naturally occurring fall of blood pressure during sleep (Fig. 9). There are, however, some patients who develop marked nocturnal hypotension even without any medication (presumably due to defective cardiovascular autoregulation), as can be seen in Fig. 8.

5.2.2.3. Conclusion. From this brief discussion, the great complexity of mechanisms of development of NA-AION, and the role of nocturnal hypotension in it become clear. A whole host of systemic and local factors, acting in different combinations and to different extents may derange the ONH circulation, with some making the ONH susceptible to ischemia and others acting as the final insult. Nocturnal hypotension seems to be an important precipitating factor in the susceptible patient.

The pathogenesis of NA-AION is complex but not, as often stated, unknown.

Recently Levin and Danesh-Meyer (2008) have published a hypothesis dealing with pathogenesis of NA-AION. According to this hypothesis, "Anatomical or functional occlusion of CRV (central retinal vein) tributaries within the anterior optic nerve would cause venous congestion of the optic nerve parenchyma, subsequent cytotoxic and vasogenic edema, and consequent further compression of venules feeding the CRV. Venous congestion can cause secondary constriction of small arterioles via the venoarteriolar response." Based on my studies on the anatomy and blood of the optic nerve, and experimental and clinical studies on various aspects of NA-AION and central retinal vein occlusion, I find this hypothesis invalid on several counts (Hayreh, in press b). Venous occlusion has no role whatsoever in the development of NA-AION.

5.2.3. NA-AION and cerebral stroke are not similar in nature

There is a common perception among ophthalmologists and neurologists that NA-AION and cerebral stroke are similar in nature pathogenetically and in management. This has resulted in major controversy on pathogenesis and management of NA-AION. The following evidence, however, indicates that NA-AION pathogenetically is a distinct clinical entity.

5.2.3.1. Difference in association of smoking. There is a huge volume of literature showing a significant association between smoking and cerebrovascular accident (a thromboembolic disorder) (Dagenais et al., 2005). No association has been found between smoking and NA-AION (Newman et al., 2002; Hayreh et al., 2007).

5.2.3.2. Difference in response to aspirin. While the beneficial effect of aspirin in cerebrovascular accident (usually a thromboembolic disorder) is well-established, NA-AION studies have shown that aspirin has no beneficial effects in NA-AION (being a hypotensive disorder) (Newman et al., 2002; Beck et al., 1997; Botelho et al., 1996).

5.2.3.3. Difference in association between thrombophilic risk factors. While an association has been reported between thrombophilic risk factors and cerebrovascular accident, no significant association has been found between NA-AION and thrombophilic risk factors for the same reason (Salomon et al., 1999; Hayreh, 2001a, 2008e; Abu-Amero and Bosley, 2006).

5.2.3.4. A hypotensive disorder. As discussed above, other findings show that NA-AION is primarily a hypotensive disorder and not a thromboembolic disorder in the vast majority.

5.2.4. Histopathologic findings in ischemic optic neuropathy

Knox et al. (2000) reported these in 193 eyes with ischemic optic neuropathy. They concluded, "ischemic optic nerve lesions are initially acellular and later show macrophage infiltration. Cavernous lesions with MPS (mucopolysaccharide) are present 4 weeks or longer after vision loss. The location of MPS posteriorly and along the internal margin suggests that MPS is produced at the edges of lesions." The experimental model of AION by Hayreh and Baines (1972) showed similar histopathological findings (Fig. 10).

5.2.5. Clinical features of classical NA-AION

NA-AION is the most common type of ischemic optic neuropathy. It usually has classical symptoms and signs which make it easy to diagnose. The subject is discussed at length elsewhere (Hayreh, 1996). Following is a very brief account of the clinical features of NA-AION.
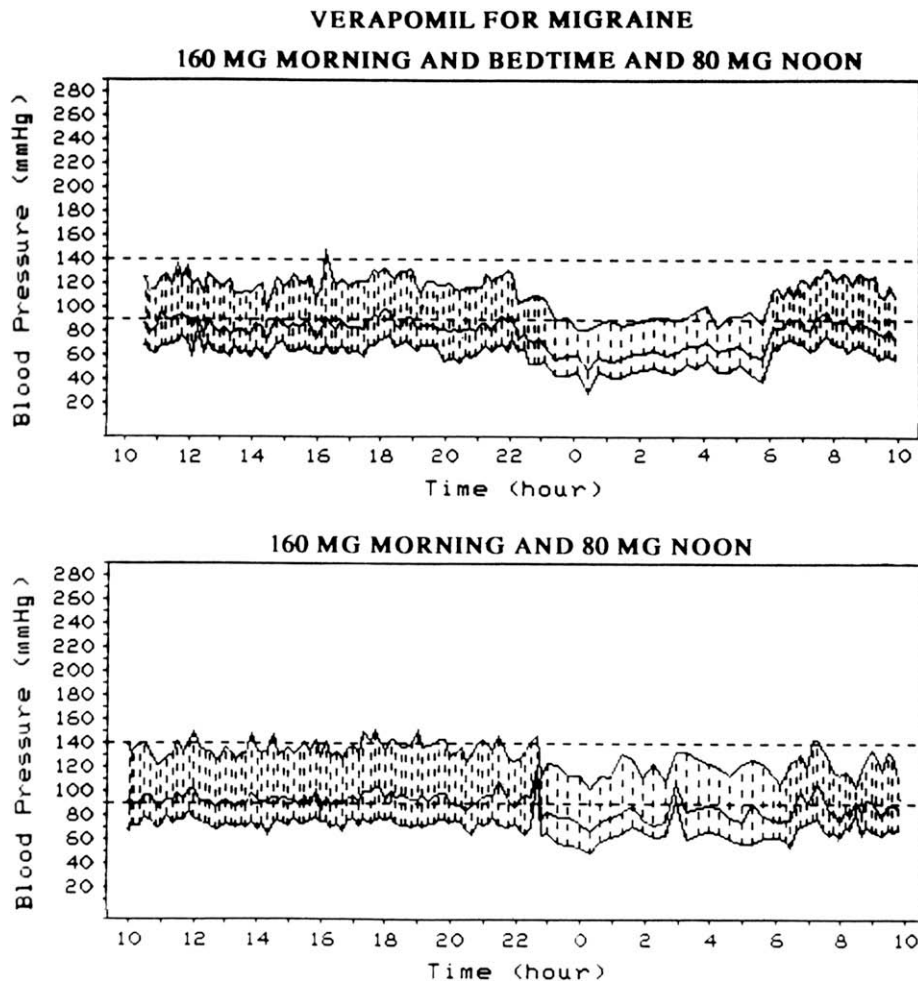
Fig. 9. Two 24-h ambulatory blood pressure monitoring records (based on individual readings), starting at 10 a.m., of a 63-year old woman taking Verapamil hydrochloride for migraine. Both records show normal blood pressure during the waking hours. The upper record, when she was taking Verapamil at bedtime, shows that during sleep there was a marked degree of nocturnal arterial hypotension (blood pressure falling as low as 80/30 mmHg). The lower record shows markedly less nocturnal hypotension on stopping the bedtime dose of Verapamil (lowest blood pressure 110/50 mmHg). (Reproduced from Hayreh, 2008c).

5.2.5.1. Incidence of NA-AION. A population-based study in the state of Missouri and Los Angeles County, CA, USA, found that among persons 50 or older the estimated mean annual incidence rate of NA-AION was 2.30 per 100,000 populations, and it was significantly higher among white individuals than black or Hispanics (Johnson and Arnold, 1994). Another epidemiological study in the population of Olmsted County, MN, USA, in persons 50 and older, reported the incidence of NA-AION as 10.2 per 100,000 individuals (Hattenhauer et al., 1997). Such a large discrepancy between the two studies indicates the problems of obtaining reliable information.

5.2.5.2. Age, gender and racial features. NA-AION is mostly a disease of the middle-aged and elderly, although no age is immune from it. In a study of 624 patients with NA-AION, mean ± SD age was 61.0 ± 12.3 SD; range 18–100 years, with 11% in young (<45 years), 49% in middle- aged (45–64 years) and 40% in the elderly (≥65 years) persons (Hayreh et al., 2007). In another study of 727 consecutive patients with NA-AION, 23% were younger than 50 years (median 43 years; range, 13– 49 years) (Preechawat et al., 2007). Thus, the prevalent impression that NA-AION is a disease only of the elderly not correct – no age is immune from NA–AION. It is seen somewhat more often in men than in women – in one study the ratio was 59 versus 41% (Hayreh et al., 2007) and in another study 58 versus 42% (Preechawat et al., 2007). It is far more

common among the white population than in other racial groups (Johnson and Arnold, 1994; Hayreh et al., 2007; Preechawat et al., 2007).

5.2.5.3. Symptoms. In the vast majority, these are typical. There is a sudden and painless deterioration of vision, usually discovered on waking in the morning (Hayreh et al., 1997b). When there is progressive visual loss, the patients again usually notice it on waking in the morning. Some patients may complain of intermittent blurring of vision when the visual field defect passes through the fixation point because of unconscious shifting of fixation between the seeing and the blind areas near the fixation (Fig. 11). NA-AION patients often complain of loss of vision towards the nose and less commonly altitudinal loss. Later on, photophobia is a common complaint, particularly in bilateral cases. Some patients may complain of simultaneous onset of visual loss in both eyes; however, in my study of more than a thousand patients with NA-AION, the perceived "simultaneous" visual loss in both eyes usually occurred because the patient was unaware of the prior visual loss in the first eye and discovered it only when the second eye became involved. Simultaneous bilateral onset of NA-AION is extremely rare.

5.2.5.4. Visual acuity. In a study of 500 consecutive NA-AION eyes, when patients were seen within 2 weeks after the onset of visual
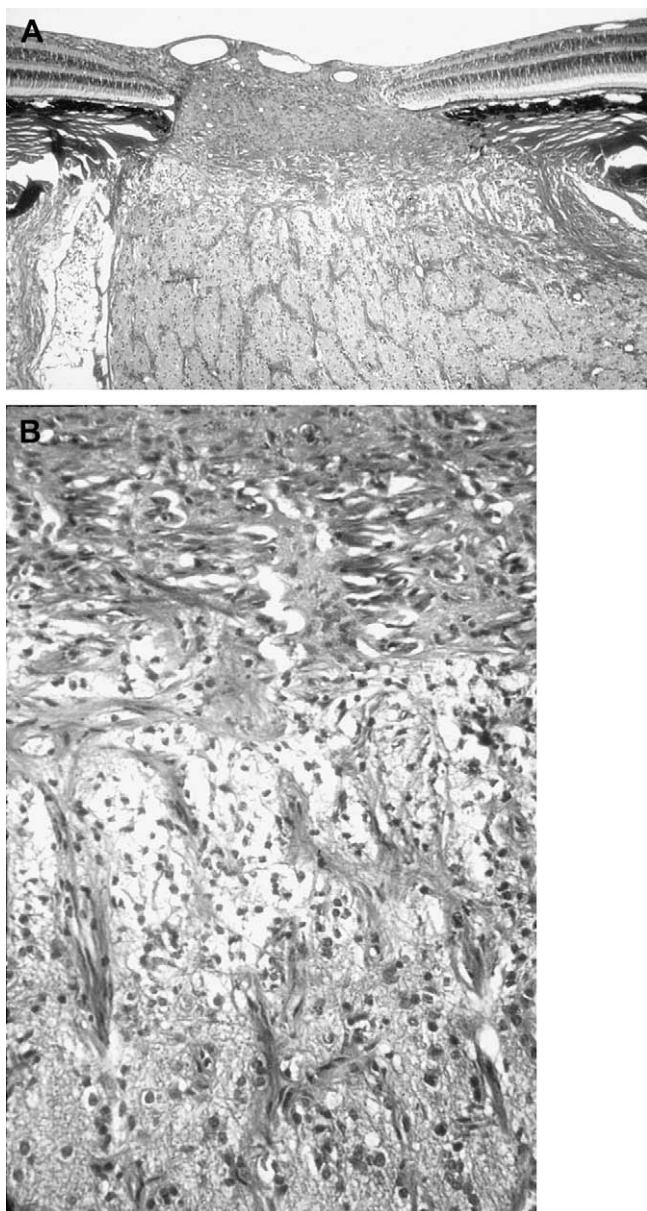
Fig. 10. Photomicrographs of the optic nerve head and retrolaminar optic nerve in rhesus monkey 36 days after occlusion of all PCAs (Masson's Trichrome stain) showing: (**A**) atrophy and degenerative changes in retrolaminar region, and (**B**) higher magnification showing marked degeneration of neural tissue in retrolaminar region, producing an appearance resembling cavernous degeneration. (Reproduced from Hayreh and Baines, 1972).

loss, initial visual acuity was 20/20 in 33%, better than 20/40 in 51%, and 20/200 or worse in 21% (Hayreh and Zimmerman, 2008a,b). This shows that the presence of normal visual acuity does not rule out NA-AION. Comparison of refraction in NA-AION patients 50 years and older with that of an age-matched general population showed no significant difference between the two groups (Hayreh and Zimmerman, 2008d).

5.2.5.5. Visual fields. In contrast to visual acuity, which can be within normal limits in almost half of the eyes with NA-AION, visual field defects are a universal occurrence. Therefore, perimetry is the most important and essential visual function test to evaluate the visual loss. These eyes can present with a variety of optic nerve related visual field defects. In a visual field study of 312 consecutive NA-AION eyes, manual kinetic perimetry (i.e. visual fields plotted

with a Goldmann perimeter) showed an overall prevalence of general visual field defects in 83% with I-2e, 79% with I-4e and 69% with V-4e, and of scotoma(s) within the central 30° in 55, 49 and 36% respectively (Hayreh and Zimmerman, 2005). Central scotoma was seen in 49% with I-2e, 44% with I-4e, and 29% with V-4e. Relative inferior altitudinal defect was common (35% with I-2e; and 22% with I-4e), but absolute inferior altitudinal defect was seen in only 8%. By contrast, absolute inferior nasal sector visual loss was the most common defect detected in NA-AION (22%). Thus, a combination of a relative inferior altitudinal defect with absolute inferior nasal defect is the most common pattern in NA-AION (Fig. 11A). This contradicts the commonly held belief that inferior altitudinal visual field defect is typical of NA-AION.

Currently visual fields are usually plotted using automated perimetry. Unfortunately, automated perimetry provides information on only up to about 24–30° in the periphery. Kinetic perimetry, by contrast, provides peripheral visual field information all the way to about 80–90° temporally, 70° inferiorly, 60–70° nasally and 50–60° superiorly. This has two important implications.

5.2.5.5.1. Peripheral visual field defects. It is well -established that the constant tracking provided by the peripheral visual fields is essential for sensory input to our day-to-day activity. For example, the peripheral visual field is vital for driving and "navigating" in the world. In view of that, to assess the visual function disability produced by NA-AION, it is important to have complete information about the peripheral visual fields and any impairment in them. While kinetic perimetry provides that information reliably, automated perimetry does not. This is big drawback in automated perimetry to evaluate visual function in NA-AION.

5.2.5.5.2. Central visual field defects. Large scotomas in the central 24–30° on automated perimetry may be misinterpreted as altitudinal when in fact the eye still may have intact peripheral field outside the central 24–30°. This may be a factor in the widespread erroneous belief that inferior altitudinal field defect is the most common defect in NA-AION.

Therefore, in NA-AION the visual field plotted with manual kinetic perimetry provides far superior information about type of visual field defect and the peripheral field, and for evaluating visual functional disability (Hayreh and Zimmerman, 2005).

5.2.5.6. Natural history of visual outcome in NA-AION. There are two prospective studies that have evaluated this, one based on 125 eyes (Ischemic Optic Neuropathy Decompression Trial Research Group, 1995) and the other on 386 eyes (Hayreh and Zimmerman, 2008a); both arrived at the same conclusion. Both studies showed that in patients seen within 2 weeks of onset of visual loss and initial visual acuity of 20/70 or worse, there was improvement in 41–43% and worsening in 15–19% at 6 months. One of these studies that evaluated visual fields with kinetic perimetry showed that 26% of those who were first seen ≤2 weeks of onset with moderate to severe visual field defect, showed improvement at 6 months (Hayreh and Zimmerman, 2008a). Visual acuity and visual fields showed improvement or further deterioration mainly up to 6 months, with no significant change after that (Hayreh and Zimmerman, 2008a). When NA-AION develops in the second eye, there is no correlation in the visual outcome in the two eyes.

5.2.5.7. Anterior segment of the eye. This invariably shows no abnormality except for the presence of relative afferent pupillary defect in unilateral NA-AION eyes, and in some there may be raised IOP.

5.2.5.8. Optic disc changes. At the onset of visual loss, there is always optic disc edema (ODE) (Hayreh and Zimmerman, 2007b). There are several misconceptions about ODE in NA-AION. The most
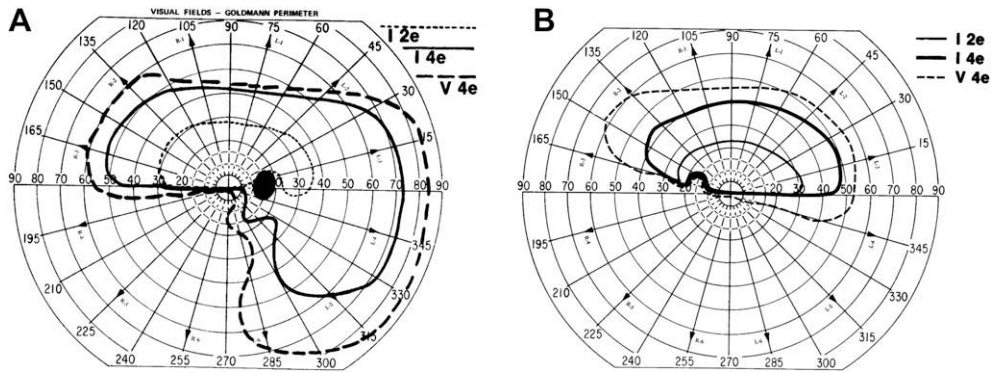
Fig. 11. Visual field defects in NA-AION, plotted with Goldmann perimeter (using I-2e, I-4e and V-4e targets). (**A**) Shows inferior altitudinal defect with I-2e and inferior nasal defect with I-4e and V-4e. (**B**) Shows absolute inferior altitudinal defect with I-2e, I-4e and V-4e. The visual acuity in both eyes was 20/20. (Reproduced from Hayreh and Zimmerman, 2005).

common one is that in NA-AION the ODE is always pale – that is not true at all initially, because the color of ODE in NA-ION initially does not differ from ODE due to other causes – in some cases there may even be hyperemia of the optic disc (Figs. 12, 13 and 14B). A splinter hemorrhage at disc margin is common (Fig. 13). ODE starts to develop pallor about 2–3 weeks after the onset of NA-AION (Hayreh and Zimmerman, 2007b). A study based on evaluation of various aspects of ODE in 749 eyes showed that the overall median time (25th–75th percentile) to spontaneous resolution of ODE from the onset of visual loss was 7.9 (5.8 – 11.4) weeks (Hayreh and Zimmerman, 2007b). The time it took to resolve depended on several factors, e.g., longer in diabetics than in non-diabetics, and worse initial visual field defect and visual acuity were associated with a faster resolution of ODE. When patients were treated with steroid therapy within 2 weeks after onset of NA-AION, there was a significantly faster ODE resolution than in the untreated cases. There is a characteristic evolutionary pattern of ODE in NA-AION (Hayreh and Zimmerman, 2007b). Initially the involved part of the disc (i.e. corresponding to the location of visual field loss) has edema, with the rest of the disc normal or showing much less edema → after several days the entire disc may show generalized

edema → still later, the optic disc in the originally involved part begins to develop pallor and the edema gradually starts to regress in that part, so that the uninvolved part (corresponding to normal visual field) may have more edema than the ischemic part → then the involved part has pallor but is not edematous any more, while the rest of the disc may show mild edema and even some pallor → the ODE gradually resolves → pallor of the involved region only or the entire disc (Fig. 14), and in the latter case the pallor may or may not be more marked in the involved part. Therefore, the sector of the optic disc showing edema usually corresponds to the location of the visual field defect only during the very early stage, and not later on. Similarly, Arnold and Hepler (1994b) recorded "no consistent correlation" of the sector of the disc edema with the visual field defect. On resolution of ODE, the distribution of optic disc pallor does not always correspond with the extent and location of visual and nerve fiber loss (Hayreh and Zimmerman, 2007b).

In the fellow normal eye, optic disc usually shows either no cup or small cup (see above). This can be a helpful clue in the diagnosis of NA-AION in doubtful cases. If originally both eyes have small disc cups, I have seen that in unilateral NAION, once the disc edema
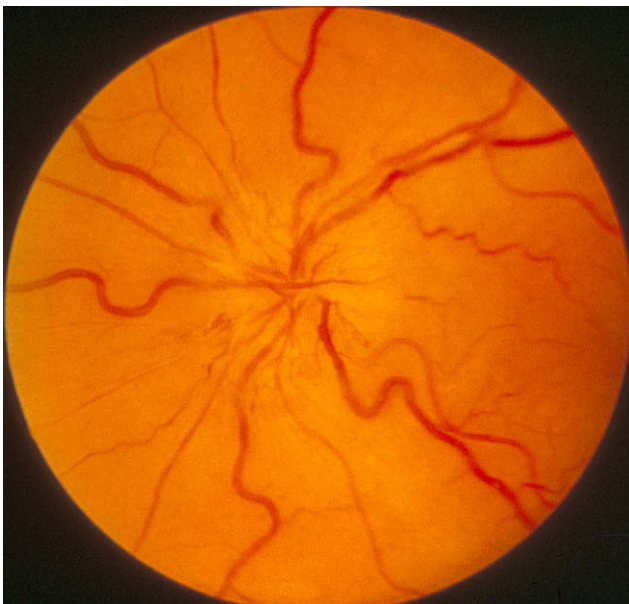

Fig. 12. Left fundus photograph showing optic disc edema and hyperemia during the acute phase of NA-AION.
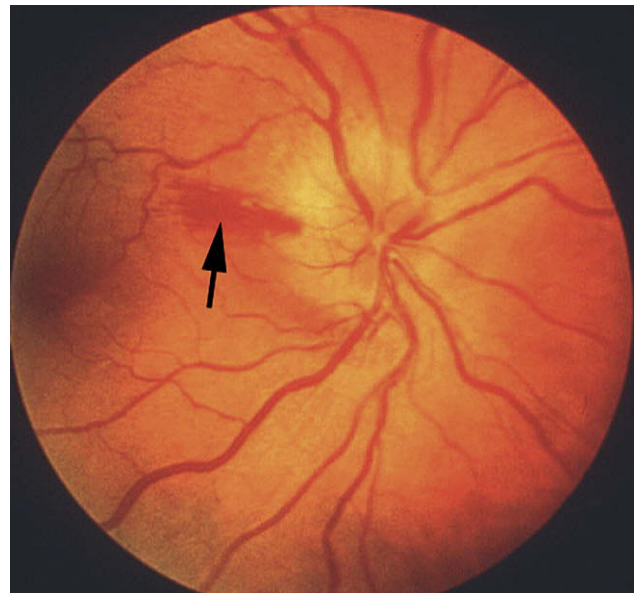

Fig. 13. Right fundus photograph showing optic disc edema and hyperemia, with a splinter hemorrhage (arrow) during the acute phase of NA-AION.
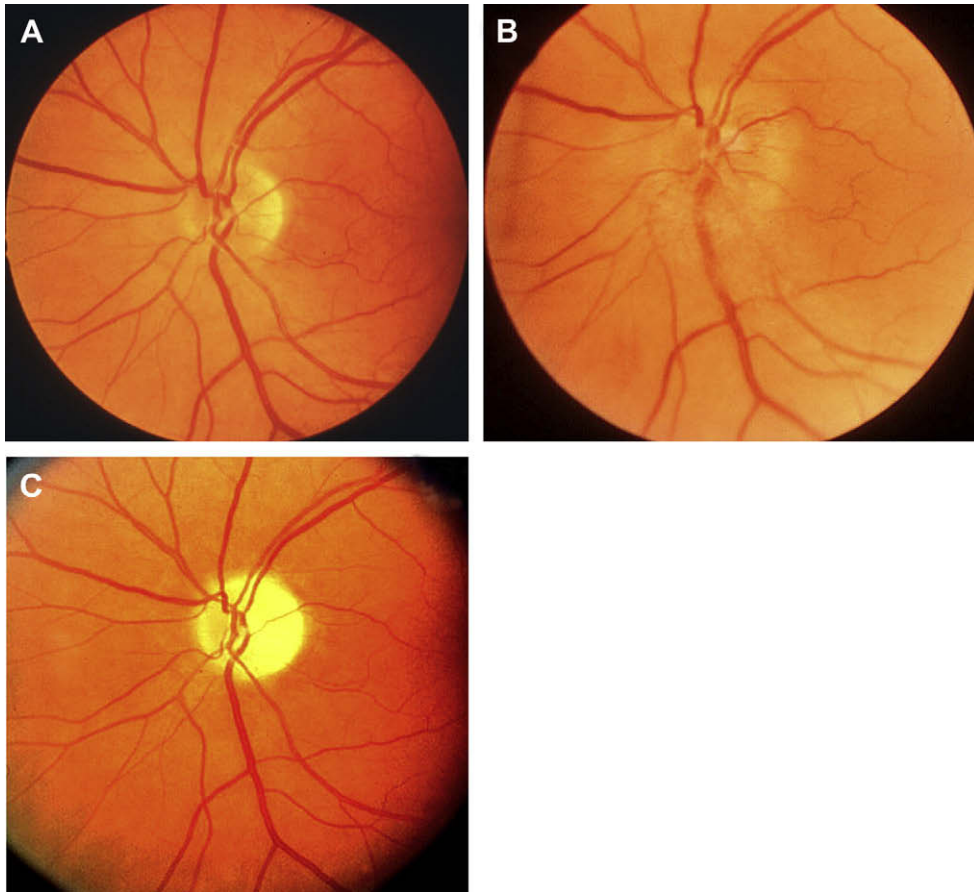
Fig. 14. Fundus photographs of left eye of a 53-year-old man. (**A**) Normal disc before developing NA-AION, (**B**) with optic disc edema during the active phase of NA-AION, and (**C**) after resolution of optic disc edema and development of optic disc pallor – more marked in temporal part than nasal part.

resolves, the cup in the involved eye may become slightly larger than the fellow eye because of loss of nerve fibers. This has also been reported by others (Saito et al., 2008).

In occasional cases, where NA-AION is due to embolism into the PCA, the ODE, unlike in the classical NA-AION, usually has a chalky white appearance.

In diabetics, optic disc changes in NA-AION may have some characteristic diagnostic features. During the initial stages, the ODE

is usually (but not always) associated with characteristic prominent, dilated and frequently telangiectatic vessels over the disc, and much more numerous peripapillary retinal hemorrhages than in non-diabetics (Fig. 15A) (Hayreh and Zahoruk, 1981; Hayreh and Zimmerman, 2008c). These findings may easily be mistaken for proliferative diabetic retinopathy associated with optic disc neovascularization. When the ODE resolves spontaneously, these prominent telangiectatic disc vessels and retinal hemorrhages also

Fig. 15. Fundus photographs of the left eye, of a 19½ year-old white male juvenile diabetic. (**A**) Shows massive optic disc edema with marked telangiectatic vessels on the optic disc, multiple punctate peripapillary and macular retinal hemorrhages, engorged retinal veins. (**B**) Shows normal-looking optic disc, no abnormal vessels on the disc, and no retinal hemorrhages on resolution. (Reproduced from Hayreh, 1978b).

resolve spontaneously (Fig. 15B). The presence of these characteristic fundus changes in some diabetics with NA-AION has resulted in a good deal of controversy bec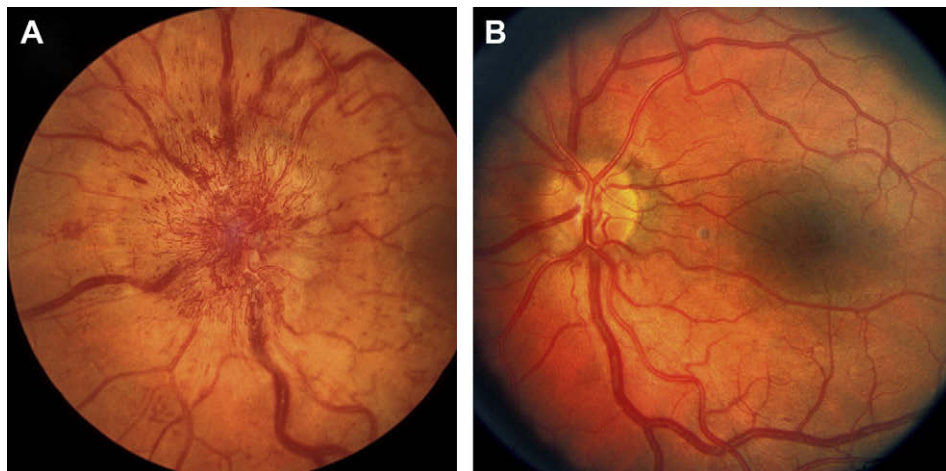ause it has been thought to be a separate clinical entity – described under different eponyms, the most common being "diabetic papillopathy", when in fact it is NA-AION (Hayreh and Zimmerman, 2008c).

5.2.5.9. Other fundus changes. The presence of a few splinter hemorrhages on optic disc or immediate peripapillary region is common in association with the ODE (Fig. 13); those resolve spontaneously with ODE resolution. Diabetics tend to have more peripapillary retinal hemorrhages than non-diabetics. (Hayreh and Zahoruk, 1981; Hayreh and Zimmerman, 2008c). Occasionally, I have seen mild serous retinal detachment between the optic disc and macula and that may even extend to the macular region to produce macular edema (Fig. 16). This has also been reported by other authors (Tomsak and Zakov, 1998; Hedges et al., 2008). Because of ODE, there is a certain amount of retinal venous engorgement. In some eyes, as the ODE resolves, some lipid deposits are seen in the peripapillary or macular region.

5.2.5.10. Fluorescein fundus angiographic findings. It is only angiography during the very early arterial phase of dye filling in the fundus that demonstrates the tell-tale impaired circulation and its location in NA-AION. In my studies, there is almost invariably filling defect/delay in the prelaminar region and in the peripapillary choroid (Fig. 7) and/or choroidal watershed zones (Figs. 5A,B,D) at onset of NA-AION (Hayreh, 1985). This has also been shown by others (Arnold and Hepler, 1994a; Arnold et al., 1996). In the occasional case, where NA-AION is due to embolism into the PCA, the part of the choroid supplied by the occluded PCA or short PCA does not fill (Fig. 4A). Late optic disc staining is a non-specific finding of optic disc edema, and has no diagnostic importance for NA-AION.

5.2.5.11. Bilateral NA-AION. The cumulative probability of the fellow eye developing NA-AION has varied among different studies:

25% within 3 years in 438 patients (Beri et al., 1987), 17% in 5 years in 431 patients (Beck et al., 1997) and 15% over 5 years in 326 patients (Newman et al., 2002); however, different criteria were used to determine the probability, which may explain the differences. According to one study (Beri et al., 1987), the risk is greater in men, particularly young diabetic men, while according to another study (Newman et al., 2002) increased incidence was associated with poor baseline visual acuity and diabetes mellitus. The risk of the second eye getting involved by NA-AION was evaluated in 655 patients (206 diabetics and 449 non-diabetics) and that showed a significantly ($p = 0.003$) greater risk in diabetics than in non-diabetics (Hayreh and Zimmerman, 2008c); that study also showed that the median (25th–75th percentile) time to involvement of the fellow eye by NA-AION was 6.9 (0.4–16.9) years in diabetics and 9.1 (1.8–19.0) years in non-diabetics.

There are reports in the literature of simultaneous onset of bilateral NA-AION. As discussed above, in my study of more than a thousand patients with NA-AION, the reported "simultaneous" visual loss in both eyes due to NA-AION usually occurred because the patient was unaware of the NA-AION in the first eye until the second eye got involved. Pattern of ODE during the initial stages of NA-AION is different from that later on (see above), and that is helpful to time the onset in bilateral NA-AION. Simultaneous bilateral onset of NA-AION is extremely rare, except in patients who develop sudden, severe arterial hypotension, e.g. during hemodialysis or surgical shock.

5.2.5.12. Recurrence of NA-AION in the same eye. Such recurrences mentioned in the literature are often more a progression of NA-AION during the acute stage rather than actual new episodes after the first episode has resolved completely. In a study of 829 NA-AION eyes, the overall cumulative percentage of recurrence of NA-AION in the same eye was at 3 months $1.0 \pm 0.4\%$ (SE), at 6 months $2.7 \pm 0.7\%$, at 1 year $4.1 \pm 0.9\%$, and 2 years $5.8 \pm 1.1\%$ (Hayreh et al., 2001). The only significant association for recurrence of NA-AION
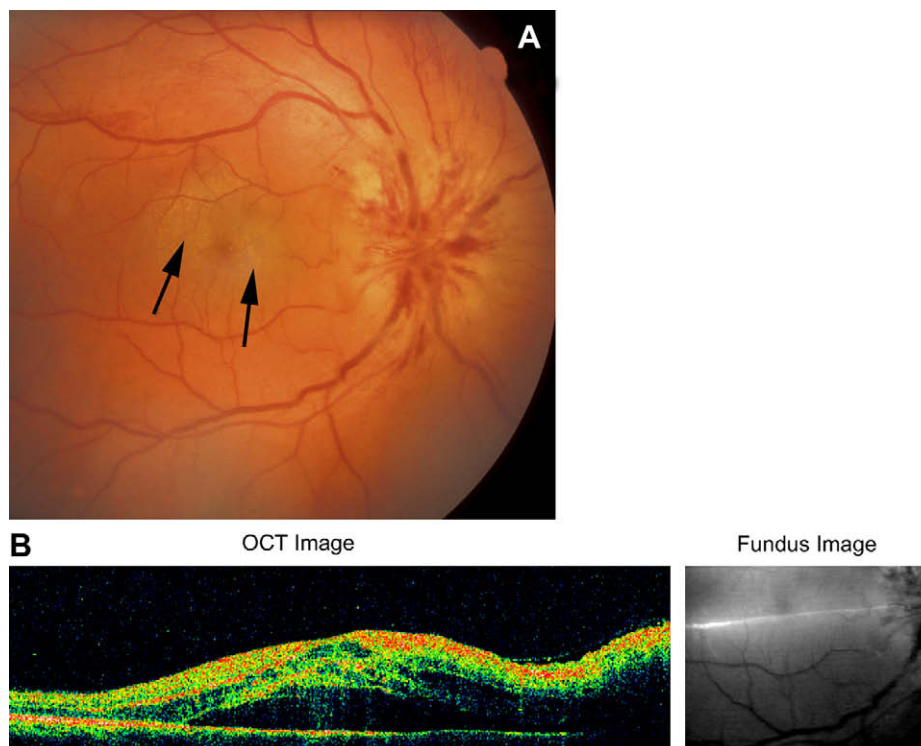

Fig. 16. Fundus photograph (**A**) and OCT (**B**) of right eye with NA-AION and serous retinal detachment between the optic disc and the macula. In (**A**) arrows indicate the presence of lipid deposits in the central part of the macula.

was with nocturnal arterial hypotension. Thus, this study indicated that nocturnal diastolic arterial hypotension might be a risk factor for recurrence of NA-AION; however, since NA-AION is a multifactorial disease, other risk factors so far unknown may also play a role.

5.2.5.13. NA-AION in diabetics versus non-diabetics. In a study of 655 consecutive NA-AION patients (931 eyes) – 206 patients with diabetes and 449 without – comparison of various clinical features of NA-AION in diabetics and non-diabetics showed no significant difference in age, but diabetics had slightly more women than men (45 versus 38%; $p = 0.078$), and a higher prevalence of arterial hypertension ($p < 0.0001$), ischemic heart disease ($p = 0.0001$), transient ischemic attacks ($p = 0.0003$), and second eye involvement by NA-AION ($p = 0.003$) (Hayreh and Zimmerman, 2008c). Initial visual acuity did not differ significantly between diabetics and non-diabetics; however, of those seen within 2 weeks of onset of NA-AION, diabetics had less severe visual field defect ($p = 0.010$). At 6 months after onset, there was no significant difference in visual acuity and visual field improvement between diabetics and non-diabetics. Time to optic disc edema resolution was ($p = 0.003$) longer in diabetics than non-diabetics. As discussed above, the ODE in diabetics usually has characteristic, diagnostic dilated telangiectatic vessels during early stages of NA-AION.

5.2.5.14. NA-AION and phosphodiesterase-5 (PDE5) inhibitors. The subject is discussed at length elsewhere (Hayreh, 2005; Hayreh, 2008c). Briefly, most patients reported to have developed NA-AION following the use of these drugs are middle-aged or elderly men who already had various predisposing risk factors for NA-AION (see above). These drugs are mostly taken in the evening for sexual intercourse. PDE5 inhibitors result in fall of blood pressure; when taken in the evening, as discussed above, there is high chance of them producing abnormal nocturnal arterial hypotension, which may be further aggravated if the person is taking other arterial hypotensive drugs for arterial hypertension or other cardiovascular disorders. Like the vast majority of NA-AION patients, most of the patients reporting NA-AION following ingestion of PDE5 discovered visual loss upon awakening in the morning. A critical review of all the reported cases shows a usually good temporal relationship between the ingestion of these drugs and onset of NA-AION. When all the above evidence is put together, it suggests that Viagra and other PDE5 inhibitors can result in development of NA-AION in persons who already have predisposing risk factors.

5.2.5.15. Amiodarone and NA-AION. There is a universal belief that amiodarone causes optic neuropathy, called "amiodarone-induced optic neuropathy". However, the following facts do not support that view (Hayreh, 2006).

(i) Patients who take amiodarone have cardiovascular disorders, which are *per se* well-established risk factors for the development of NA-AION (Hayreh et al., 1994b, 1996). Many of these patients also have other risk factors (arterial hypertension, diabetes mellitus, hyperlipidemia and ischemic heart disease) (Hayreh et al., 1994b; Hayreh, 1996). They are candidates for NA-AION whether they are taking amiodarone or not.
(ii) Patients on amiodarone often also take other drugs (beta-blockers, calcium channel blockers, ACE inhibitors) that influence the cardiovascular system. As discussed above, patients on these drugs are at high risk of developing nocturnal arterial hypotension, which is a common precipitating factor for the development of NA-AION (Hayreh, 1996; Hayreh et al., 1994c, 1999).
(iii) One of the arguments put forward to differentiate amiodarone-induced optic neuropathy from NA-AION is that some patients taking amiodarone develop asymptomatic ODE that

may later progress to visual loss. Asymptomatic ODE has been known since 1981 as an early sign of NA-AION (Hayreh, 1981a) and a recent paper reported 60 eyes with "incipient NA-AION" that had asymptomatic ODE to begin with (Hayreh and Zimmerman, 2007a). Many of them progressed to visual loss, but not all. Not one of those patients was taking amiodarone. ODE for various reasons can persist much longer than the 6–8 weeks usually seen for typical NA-AION (Hayreh and Zimmerman, 2007b). Moreover, there are reports of patients with asymptomatic ODE progressing to visual loss after amiodarone had been discontinued (Murphy and Murphy, 2005).
(iv) Most importantly, the clinical features of the optic neuropathy in patients taking amiodarone are typical of NA-AION rather than a toxic optic neuropathy.

Thus, in the multifactorial scenario of NA-AION, it is the systemic cardiovascular risk factors rather than amiodarone that cause NA-AION.

5.2.5.16. Familial NA-AION. There are five reports in the literature representing 10 unrelated families in which more than one member developed NA-AION (Berggren et al., 1974; Manor, 1990; Wang et al., 1999; Fingert et al., 2007; Hayreh et al., 2008). Hayreh et al. (2008) have shown that this rare entity of familial NA-AION is clinically similar to the classical non-familial NA-AION, with the exception that familial NA-AION occurred in younger patients and had much higher involvement of both eyes than the classical NA-AION. The role of genetic factors in familial NA-AION is not known. In fact, it could be argued that since NA-AION is a common disease, the possibility of occasional occurrence of clusters in families without any genetic abnormality cannot be ruled out. The potential role of genetic factors in familial NA-AION remains to be clarified by additional research. One preliminary study has suggested that the G4132A mitochondrial mutation may be associated with disease in at least one pedigree with familial NA-AION (Fingert et al., 2007), but the report by Hayreh et al. (2008) indicates that this mutation is not associated with disease in two of the three familial NA-AION pedigrees in the study, nor is this mutation associated with the much more common classical non-familial NA-AION.

5.2.6. Management of NA-AION

This has been a highly controversial subject. A number of treatments have been advocated, principally the following.

5.2.6.1. Optic nerve sheath decompression. Sergott et al. (1989) claimed that optic nerve sheath decompression improved visual function in "progressive" NA-AION. But from various studies on different basic aspects of the subject, Hayreh (1990c) concluded that there was no scientific rationale for doing optic nerve sheath decompression in NA-AION and that the procedure can be harmful. After the report by Sergott et al. (1989) and a few other anecdotal reports (Kelman and Elman, 1991; Spoor et al., 1991), the procedure gained world-wide favor not only in "progressive" but also in all types of NA-AION. A multicenter clinical trial conducted by the National Institutes of Health subsequently established that this procedure is "not effective" and "not an appropriate treatment for non-arteritic AION" and "may be harmful", because 24% of the eyes with the optic nerve sheath decompression suffered further visual loss as compared to only 12% simply left alone (Ischemic Optic Neuropathy Decompression Trial Research Group, 1995). This study also showed that 42% of cases showed improvement in visual acuity spontaneously, without any procedure.

5.2.6.2. Aspirin. One study, based on 131 patients, claimed that aspirin prevented the development of NA-AION in the fellow eye (Sanderson et al., 1995). A much larger study, based on 431 patients

with unilateral NA-AION, revealed no long-term benefit from aspirin in reducing the risk of NA-AION in the fellow eye (Beck et al., 1997). Similarly, Newman et al. (2002) found no association between regular aspirin use and incidence of new NAION in the fellow eye. Botelho et al. (1996) also found that use of aspirin does not improve the visual outcome in NA-AION patients. These findings are not surprising since NA-AION is NOT a thromboembolic disorder but a hypotensive disorder and aspirin has no effect on the blood pressure or nocturnal arterial hypotension.

5.2.6.3. Systemic corticosteroid therapy. Two small reports almost four decades ago suggested that systemic corticosteroids given during the very early stages of the disease may help to improve the visual function in some patients (Foulds, 1970; Hayreh, 1974d) However, there was a good deal of skepticism in the neuro-ophthalmic community about any use of steroid therapy in NA-AION. A recent large, prospective study (Hayreh and Zimmerman, 2008b), based on 696 eyes, comparing the visual outcome in treated (364 eyes) versus untreated control (332 eyes) groups, suggested that NA-AION eyes treated during the acute phase (i.e. so long as ODE was present) with systemic corticosteroids had a significantly higher probability of improvement in visual acuity ($p = 0.001$) and visual field ($p = 0.005$) compared to the untreated group. In eyes with initial visual acuity of 20/70 or worse, seen within 2 weeks of onset, there was visual acuity improvement in 70% in the treated group compared to 41% in the untreated group (odds ratio of improvement: 3.39; 95% CI:1.62, 7.11; $p = 0.001$). Similarly, among those seen within 2 weeks of NA-AION onset with moderate to severe initial visual field defect, there was improvement in 40% of the treated group and 25% of the untreated group (odds ratio: 2.06, 95% CI: 1.24, 3.40; $p = 0.005$). In both treated and untreated groups, the visual acuity and visual fields kept improving for up to about 6 months after the onset of NA-AION, but very little thereafter. A comparison of treated versus untreated groups also showed that ODE resolved significantly ($p = 0.0006$) faster in the treated group.

5.2.6.4. Use of intravitreal triamcinolone acetonide for treatment of NA-AION. There have recently been two contradictory studies on this topic. Jonas et al. (2007), in three patients, found that it had no beneficial effect on visual acuity. Kaderli et al. (2007), in four eyes, reported visual acuity improvement, but without any improvement in visual fields. However, the study of Kaderli et al. (2007) has some notable flaws which are discussed in detail elsewhere (Hayreh, 2008a). Briefly, these include: (a) their study was based on only four eyes. (b) Two large natural history studies have shown spontaneous visual acuity improvement in 41 – 43% of eyes with NA-AION (Ischemic Optic Neuropathy Decompression Trial Research Group, 1995; Hayreh and Zimmerman, 2008a). (c) More importantly, none of the eyes in the study by Kaderli et al. (2007) showed improvement in visual fields and all had altitudinal visual field defects. Studies have shown that in NA-AION and A-AION apparent visual acuity improvement without visual field improvement is due to the patient learning to fixate eccentrically, rather than being a genuine visual improvement (Hayreh et al., 2002; Hayreh and Zimmerman, 2008a). In Kaderli et al.'s (2007) study, eccentric fixation may explain why the visual acuity of the patients apparently improved, while the visual fields did not.

Most importantly, intravitreal triamcinolone injection in NA-AION eyes can be harmful. ONH circulation depends upon the perfusion pressure (mean blood pressure minus IOP). Intravitreal injection increases the volume in the eyeball, thereby resulting in a transient rise of IOP. In addition, there are many reports showing a substantial rise in IOP a few days or weeks after intravitreal triamcinolone. In NA-AION, with already precarious optic nerve head circulation, even a small rise in IOP for any reason can further

compromise the circulation and result in further visual loss. Oral steroid therapy for NA-AION by contrast, did not have that effect on IOP during a short-term treatment (Hayreh and Zimmerman, 2008b). Thus, one cannot equate oral and intravitreal steroid therapy in NA-AION.

5.2.6.5. Use of intravitreal Bevacizumab for treatment of NA-AION. There is an anecdotal case report claiming reduction of ODE and visual improvement after an intravitreal injection of Bevacizumab (Avastin) 3 weeks after the onset of NA-AION in one eye (Bennett et al., 2007). The authors claim that Bevacizumab – a vascular endothelial growth factor inhibitory drug – improved visual acuity in the eye by reducing ODE. It is impossible to judge the effectiveness of a mode of treatment from one eye when 41 – 43% of NA-AION eyes show spontaneous visual acuity improvement. Moreover, as discussed above, intravitreal injection causes a rise in IOP, which in an already precarious ONH circulation in NA-AION may act as the last straw to compromise the circulation and result in further loss of vision.

5.2.6.6. Reduction of risk factors. The usual advice given by ophthalmologists and neurologists to NA-AION patients is that nothing can be done. Having dealt with more than a thousand patients with NA-AION and having investigated various aspects of NA-AION over the years, I find that is an inadequate response. As discussed above, NA- AION is a multifactorial disease and many risk factors contribute to it. The correct strategy is to try to reduce as many risk factors (discussed above) as possible, to reduce the risk of NA-AION in the second eye or any further episode in the same eye.

As discussed above, nocturnal arterial hypotension is a major risk factor in NA-AION patients who already have predisposing risk factors. Since the 1960s many highly potent drugs with arterial hypotensive effect have emerged to treat arterial hypertension, other cardiovascular diseases, benign prostatic hyperplasia and other diseases; those drugs are currently widely used. It may not be coincidental that the incidence of NA-AION has progressively increased since the 1960s, so that it has now become a common visually disabling disease. This strongly suggests that NA-AION may be emerging as an iatrogenic disease, stemming from the aggressive use of the very potent arterial hypotensive agents now available. In view of this, management of nocturnal arterial hypotension seems to be an important step both in the management of NA-AION and in the prevention of its development in the second eye. Therefore, I strongly recommend that when a patient is at risk of developing ocular and ONH ischemic and vascular disorders, or has the following: (a) NA-AION or history of NA-AION in one eye; (b) active giant cell arteritis; (c) normal-tension glaucoma; (d) occlusion or severe stenosis of internal carotid artery; (e) low central retinal artery pressure; or (f) chronic ODE due to any cause, the treating physician should be made aware of the potential risks of intensive arterial hypotensive therapy, particularly giving that in the evening.

5.2.7. Incipient non-arteritic anterior ischemic optic neuropathy

Hayreh (1981a), in 1981 reported that "symptomless ODE precedes the visual loss and may be the earliest sign of AION (NA-AION)". In 2007, based on a detailed study of a series of 60 eyes with symptomless ODE, he described this as a distinct clinical entity under the name of "incipient non-arteritic anterior ischemic optic neuropathy" (Hayreh and Zimmerman, 2007a). This clinical entity initially presents with asymptomatic ODE and no visual loss attributable to NA-AION. Available evidence indicates that it represents the earliest, asymptomatic clinical stage in the evolution of the NA-AION disease process; therefore, it shares most clinical features with classical NA-AION except for the visual loss.

5.2.7.1. Clinical features of incipient NA-AION. A recent study, based on 60 eyes with incipient NA-AION, described its various clinical features. In that study, the mean (SD) age of the patients was 58.7 ± 15.9 years (range 16–85 years) (Hayreh and Zimmerman, 2007a). At initial visit, all had ODE without any visual loss attributable to NA-AION. In 55% the fellow eye had classical NA-AION, in 25% incipient progressed to classical NA-AION (after a median time of 5.8 weeks), and 20% developed classical NA-AION after resolution of a first episode of incipient NA-AION. Median time to resolution of ODE in the group that progressed was 5.8 weeks versus 9.6 weeks in those that did not. Patients with incipient NA-AION had a greater prevalence of diabetes mellitus than classical NA-AION; therefore, this has often been misdiagnosed as "diabetic papillopathy" or "diabetic papillitis", which has created confusion and controversy. Patients who progressed to classical NA-AION were significantly younger than those who did not. Similarly, incipient NA-AION progressing to classical NA-AION has also been misdiagnosed as "amiodarone-induced optic neuropathy" in patients who happen to be on amiodarone therapy for cardiovascular disorders (Hayreh, 2006).

5.2.7.2. Management of incipient NA-AION. When a patient presents with asymptomatic ODE, incipient NA-AION must be borne in mind as a strong possibility for those who have had classical NA-AION in the fellow eye, for diabetics of all ages, and for those with high risk factors for NA-AION. This can avoid unnecessary and expensive investigations.

To reduce the risk of progression of incipient to classical NA-AION, immediately steps should be taken to try to eliminate risk factors for development of NA-AION. These include the following:

1. Since nocturnal arterial hypotension is usually the precipitating risk factor in development of NA-AION by reducing the perfusion pressure in the ONH vessels, these measures should include: shifting the blood pressure lowering medicines from night or evening to morning, stopping any drugs that could cause a decrease in blood pressure during sleep (sleep medications, sedatives, alcohol, pain medications, alpha 1 blockers used for benign prostatic hypertrophy in men and bladder problems in women, and erectile dysfunction drugs.).
2. Immediate evaluation for sleep apnea, if the history indicates it.
3. If IOP is high or borderline high, it would also be advisable to try to lower IOP to improve perfusion pressure in the ONH.
4. Systemic steroid therapy may be useful. An original pilot study on incipient NA-AION suggested that systemic steroid therapy might help to reduce the risk of progression of incipient NA-AION to classical NA-AION (Hayreh, 1981a). However, the results of a subsequent study in 60 eyes showed that this therapy did not make any significant difference in the progression (Hayreh and Zimmerman, 2007a). Nevertheless, steroid therapy resulted in: (a) significantly faster resolution of ODE in the treated NA-AION group (Hayreh and Zimmerman, 2007b); and (b) a significant visual improvement in classical NA-AION compared to the natural history as discussed above (Hayreh and Zimmerman, 2008b). The disparity may be due to either nature of outcome measures being used in the two types of NA-AION, or possibly due to the much small number (60 eyes) of cases in the incipient NA-AION study compared to a much larger number (696 eyes) in the classical NA-AION.

5.2.7.3. Misconceptions about incipient NA-AION. Since this entity is more common in diabetics than non-diabetics, it has often been misdiagnosed as "diabetic papillopathy" or even "proliferative diabetic retinopathy" and treated with panretinal photocoagulation

which is not indicated and can be harmful (Hayreh and Zahoruk, 1981; Hayreh and Zimmerman, 2008c).

5.2.8. Animal model of NA-AION

A group claims that they have produced a rodent (Bernstein et al., 2003) and primate (Chen et al., 2008) animal model, which, according to them, "is clinically, angiographically, electrophysiologically, and histopathologically similar to human NAION". However, multiple flaws have been reported in that model, which invalidate their claim (Hayreh, 2008b; Hayreh, in press a).

5.2.9. Misconceptions about NA-AION

The subject of NA-AION is plagued with multiple misconceptions, resulting in controversy and confusion. Following are the major misconceptions.

1. That NA-AION and cerebral stroke are similar in nature. As discussed above, cerebral stroke is a thromboembolic disorder whereas NA-AION is primarily a hypotensive disorder.
2. That absence of optic disc cup is the main cause of development of NA-AION. As discussed above, an absent or small cup is simply a secondary contributing factor, ONCE the process of NA-AION has started, and NOT a primary factor.
3. That there is no spontaneous visual improvement in NA-AION. Two large prospective natural history studies have shown that visual acuity improves spontaneously in 41 – 43% of the eyes.
4. That NA-AION is not seen in young persons. As discussed above, two large studies have disproved this myth.
5. That all eyes with NA-AION initially have pale ODE. Disc pallor actually starts to develop only 2–3 weeks after the onset of visual loss; before that there is no pale ODE.
6. That inferior altitudinal defect is the classical diagnostic visual field defect in NA-AION. As discussed above, a study of 312 NA-AION eyes showed that inferior nasal field defect is the most common defect.
7. That all eyes with NA-AION have poor visual acuity at onset. In a study of 237 eyes seen within 2 weeks of onset, 33% had 20/20 or better visual acuity.
8. That steroid therapy has no role in the management of NA-AION. As discussed above, in a study of 696 NA-AION eyes (364 treated versus 332 controls) the treated group showed significantly more visual acuity improvement than the control group (70 versus 41%).
9. That smoking is a risk factor for development of NA-AION. Two large prospective studies have shown that this is not true.
10. That aspirin reduces the risk of second eye involvement by NA-AION. Two large studies have disproved this belief.
11. That all patients with NA-AION should be investigated for thrombophilia. As discussed above, NA-AION is not a thromboembolic disorder in the vast majority of cases.

5.3. Arteritic anterior ischemic optic neuropathy (A-AION)

This almost invariably is due to GCA, although rarely other types of vasculitis can also cause it. A-AION in one or both eyes is the most common cause of visual loss in GCA.

5.3.1. Pathogenesis

GCA is the primary cause of A-AION. Other rare causes include other types of vasculitis, e.g., polyarteritis nodosa, systemic lupus erythematosus, and herpes zoster.

GCA is a systemic vasculitis, and it preferentially involves medium-sized and large arteries. Weyand and Goronzy (2003) have recently reviewed the mechanism of disease process in GCA. According to them, GCA is a T-cell-dependent disease, and the "CD4 + T -cells that orchestrate the injury of tissues are a *sine qua*

non in the vasculitic process. T-cell activation in the non-lymphoid environment of the arterial wall requires the activation of specialized antigen-presenting cells, the dendritic cells." They go on to add, "The concept that giant-cell arteritis is the consequence of antigen-specific T-cell responses in arterial tissue implies three critical events: T-cells gain access to a site that they usually do not enter, an inciting antigen is accessible, and antigen-presenting cells that are capable of T-cell stimulation differentiate. … Tissue-resident T-cells induce and maintain inflammatory infiltrates by releasing interferon-y". It is because of this etiopathogenesis of GCA that steroid therapy may be efficacious in treatment of GCA.

In the eye, GCA has a special predilection to involve the PCA, resulting in its thrombotic occlusion. Since the PCA is the main source of blood supply to the ONH (Hayreh, 1969, 1995, 2001b), occlusion of the PCA results in infarction of a segment or the entire ONH, depending upon the area of the ONH supplied by the occluded PCA (Hayreh, 1975a). That results in development of A-AION. In a study of fluorescein angiography of 66 eyes during the early stage of A-AION, there was occlusion of the medial PCA (Fig. 4B,C and 19B) in 24, lateral PCA in five, and both medial and lateral PCAs in 37 eyes – thus medial PCA is the most commonly involved artery by GCA (Hayreh et al., 1998a). When only the medial or lateral PCA is occluded, that usually results in segmental infarction of the ONH (Figs. 4B and 19B), but when both PCAs are occluded or the occluded PCA supplies the entire ONH (Fig. 4C), that results in total infarction of the ONH. ONH ischemia is much more severe in A-AION than in NA-AION, resulting in massive visual loss in one or both eyes.

5.3.2. Clinical features of A-AION

5.3.2.1. Age, gender and race. GCA, which is by far the most common cause of A-AION, is a disease of late middle-aged and elderly persons. In the study of 85 GCA patients with A-AION by Hayreh et al. (1998a), mean $\pm$ SD age was 76.2 ± 7.0 (range 57–93 years). In that study, 71% were women and 29% men. There is evidence that GCA is far more common among Caucasians than other races; however, some cases have been reported from China, India, Thailand, Israel, among Arabs, Hispanics (Mexican) and African Americans (Hayreh and Zimmerman, 2003a). These racial differences suggest a genetic predisposition to GCA.

5.3.2.2. Symptoms. Amaurosis fugax is an important visual symptom and an ominous sign of impending visual loss in GCA. In one series, it was present in 31% of the patients (Hayreh et al., 1998a). Transient visual loss may be brought about by stooping or induced by postural hypotension. Most patients with GCA develop visual loss suddenly without any warning. Simultaneous bilateral visual loss has been reported but our study indicated that it generally represented cases where the patient is unaware of vision loss in one eye until the second eye is also involved (Hayreh et al., 1998a). The incidence of bilateral involvement depends upon how early the patient is seen, when the diagnosis is made, and how aggressively systemic corticosteroid therapy is used – the longer the time interval from the onset of visual symptoms in one eye without adequate steroid therapy, the higher the risk of second eye involvement. Other ocular symptoms in our series included diplopia in 6% and ocular pain in 8% (Hayreh et al., 1998a). I have seen a rare patient with GCA suffering from euphoria and even denying any visual loss.

GCA patients usually present with systemic symptoms, including anorexia, weight loss, jaw claudication, headache, scalp tenderness, abnormal temporal artery, neck pain, myalgia, malaise and anemia. A study, based on 363 patients who had temporal artery biopsy, showed that systemic symptoms showing a significant association with a positive temporal artery biopsy for GCA were jaw claudication (odds 9.0 times, $p < 0.0001$), neck pain (odds

3.4 times, $p = 0.0003$), and anorexia ($p = 0.0005$), with no other systemic symptoms showing significant difference from those with a negative biopsy (Hayreh et al., 1997a). Most interestingly, that study showed that 21.2% of patients with visual loss due to GCA had occult GCA, i.e. no systemic symptoms whatsoever, with a positive temporal artery biopsy and visual loss (Hayreh et al., 1998b). This is an extremely important clinical entity because there is almost a universal belief that all patients with GCA always have systemic symptoms; that has resulted in missing GCA, with tragic consequence of blindness. Thus one in five patients with GCA is at risk of going blind without any systemic symptoms of GCA at all.

5.3.2.3. Visual acuity. In one large series of 123 eyes with visual loss due to GCA, initial visual acuity was 20/40 or better in 21%, 20/50 – 20/100 in 17%, and 20/200 to count fingers in 24% and hand motion to no light perception in 38% (Hayreh et al., 1998a). Thus, although usually there is a marked deterioration of visual acuity in GCA, almost normal visual acuity does not rule it out. Visual loss in 76% of these eyes was due to A-AION.

5.3.2.4. Visual fields. The extent and severity of visual field defects depends upon the extent of optic nerve damage caused by ischemia. Compared to NA-AION, the visual defects are much more extensive and severe in A-AION.

5.3.2.5. Anterior segment of the eye. Usually it is normal except for relative afferent pupillary defect in unilateral A-AION cases. In an occasional case, there may be signs of anterior segment ischemia, with ocular hypotony, and/or marked exudation in the anterior chamber (Hayreh, 1975a) (erroneously diagnosed as anterior uveitis).

5.3.2.6. Extraocular motility disorders. This results in diplopia. The cause of involvement of extraocular muscles is controversial (Hayreh et al., 1998a). It is often thought to be due to ischemia of one or more of the three oculomotor nerves or possibly brain stem ischemia, but it seems the most likely cause is extraocular muscle ischemia caused by thrombotic occlusion of the respective muscular artery/arteries.
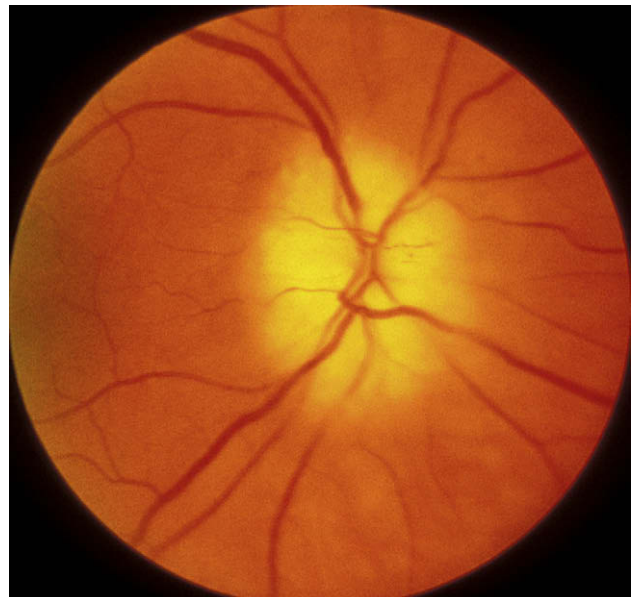

Fig. 17. Fundus photograph of right eye with A-AION showing chalky white optic disc edema during the initial stages.
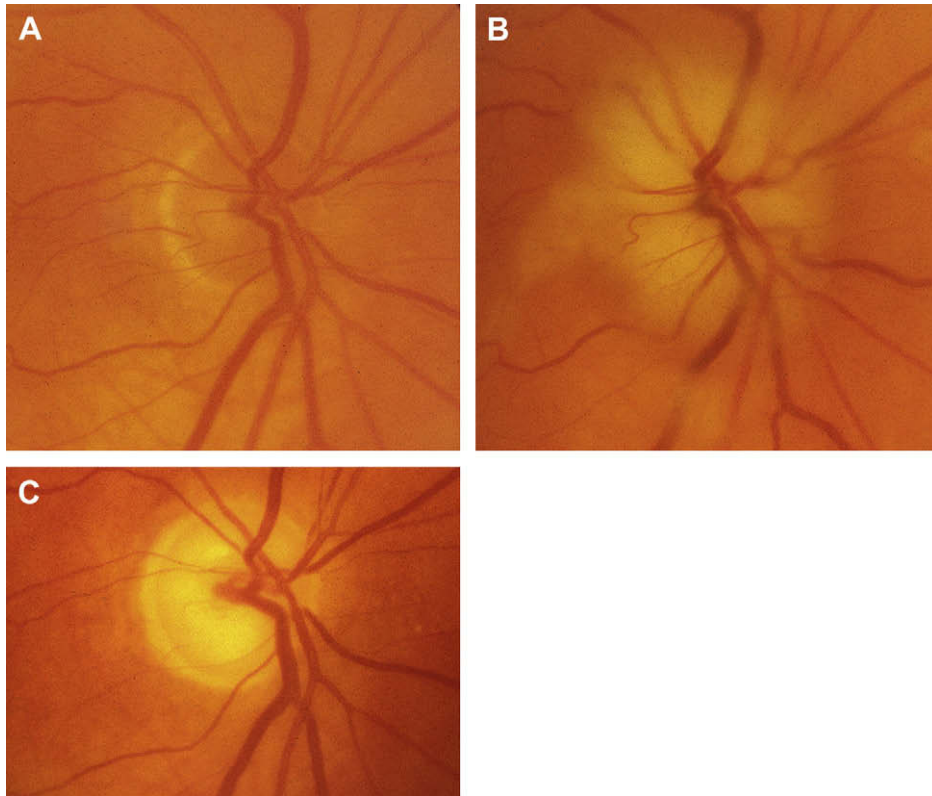
Fig. 18. Fundus photographs of right eye with A-AION: (**A**) Before developing A-AION, (**B**) 1 week after developing A-AION with chalky white optic disc edema and (**C**) 4 months later showing optic disc cupping with a cup/disc ratio of 0.8 (note no cup in **A**).

5.3.2.7. Optic disc changes. ODE, compared to NA-AION, usually has a diagnostic appearance in A-AION, i.e. chalky white color (Hayreh, 1975a, 1978b, 1998a) (seen in 69% – Hayreh et al., 1998a) (Figs. 17, 18B and 19A). When ODE resolves, the optic disc in the vast majority shows cupping indistinguishable from that seen in glaucomatous optic neuropathy (Fig. 18C) (Hayreh, 1975a, 1978b, 1998a), except that the disc rim is pale whereas it is of normal color in glaucomatous optic neuropathy. By contrast, in NA-AION no such cupping of the optic disc is seen (Hayreh, 1975a, 1978b). Danesh-Meyer et al. (2001) in a study of 92 A-AION and 102 NA-AION found optic disc cupping in 92% in A-AION and in only 2% of NA-AION. These authors (Danesh-Meyer et al., 2005) also compared cup size in involved versus the uninvolved eyes in patients with unilateral A-AION and unilateral NA-AION; in eyes affected with A-AION there was a "significant excavation and enlargement of the optic cup when compared with contralateral uninvolved eyes" but not so in NA-AION.

5.3.2.8. Other fundus changes. These are as follows in a series of 123 eyes (Hayreh et al., 1998a).

5.3.2.8.1. Retinal cotton wool spots. These were seen in one third of the eyes with visual loss. They are seen during early stages of the disease and located at the posterior pole.

5.3.2.8.2. Central retinal artery occlusion. This was seen in 14%. They are almost invariably combined with PCA occlusion – the

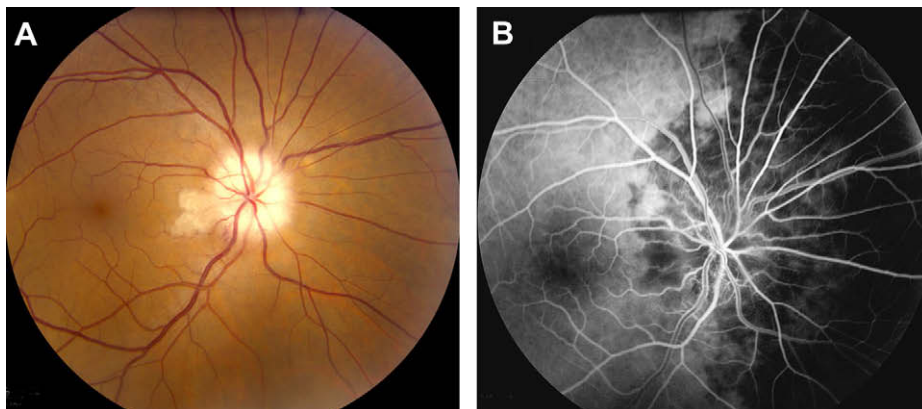**Fig. 19.** Fundus photograph (**A**) and fluorescein fundus angiogram (**B**) of right eye with A-AION and cilioretinal artery occlusion during the initial stages. (**A**) Fundus photograph shows chalky white optic disc edema with retinal infarct in the distribution of occluded cilioretinal artery. (**B**) Fluorescein fundus angiogram shows evidence of occlusion of the medial PCA and no filling of the cilioretinal artery.
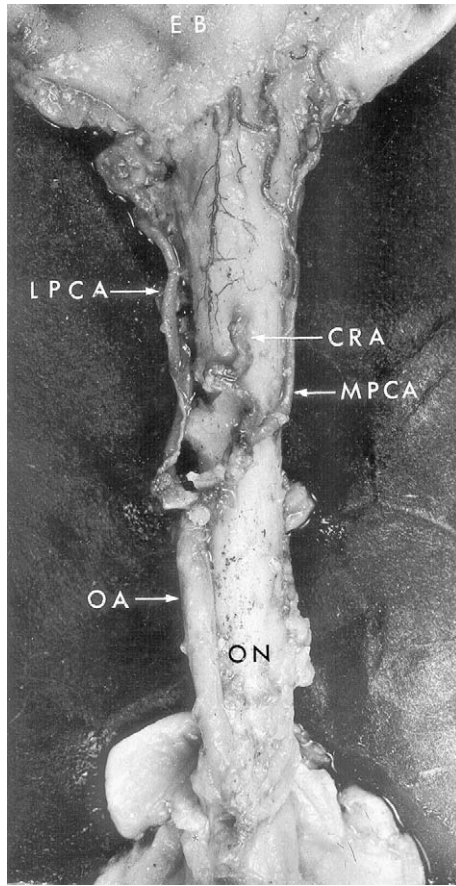
Fig. 20. Photograph of inferior surface of the intraorbital part of the optic nerve (ON) and adjacent eyeball (EB) showing ophthalmic artery (OA) with its lateral (LPCA) and medial (MPCA) posterior ciliary arteries and central retinal artery (CRA). Note a common trunk of origin of MPCA and CRA from the ophthalmic artery.

and over, it is essential to rule out GCA, to prevent catastrophic visual loss – which is preventable with adequate corticosteroid therapy (see below).

5.3.2.8.3. Cilioretinal artery occlusion. The PCA supplies the ONH (Hayreh, 1969, 1995, 2001b) as well as the cilioretinal artery, when that artery is present (Hayreh, 1963c). Occlusion of the PCA by GCA results in simultaneous development of both A-AION and cilioretinal artery occlusion (Fig. 4C and 19) (Hayreh, 1974c, 1978b, 1990a; Hayreh et al., 1998a). These eyes present with a classical, diagnostic clinical picture of GCA, i.e. a combination of chalky white optic disc edema, retinal infarct in the region of the occluded cilioretinal artery and PCA occlusion on fluorescein angiography (Fig. 19). Occlusion of the cilioretinal artery in GCA has erroneously been diagnosed as "branch retinal artery occlusion" (Fineman et al., 1996), but the so-called "branch retinal arteries" are in fact arterioles, and GCA is a disease of the medium-sized and large arteries and not of the arterioles (Hayreh et al., 1998a; Hayreh and Zimmerman, 2003a). I have seen patients with cilioretinal artery occlusion diagnosed by ophthalmologists as ordinary BRAO and left untreated, resulting in catastrophic visual loss in both eyes, which could have been prevented, if the possibility of GCA as one of its causes had been borne in mind.

5.3.2.8.4. Choroidal ischemic lesions. Occlusion of the PCA by GCA may also result in development of choroidal ischemic lesions, which are usually located in the midperipheral region of the fundus and frequently are triangular in shape, with their base toward the equator and apex toward the posterior pole (Fig. 21) (Hayreh, 1974c).

5.3.2.8.5. Ocular ischemia. GCA rarely may cause thrombosis and occlusion of the ophthalmic artery, which may result in development of ocular ischemia.

5.3.2.8.6. Fluorescein fundus angiographic findings. As discussed above, thrombosis and occlusion of the PCAs is the main lesion in GCA. This is very well demonstrated by fluorescein fundus angiography, provided it is performed soon after the visual loss (Figs. 4B,C and 19B). As time passes, choroidal filling defects tend to resolve slowly by collateral circulation. Thus, fluorescein fundus angiography during the early stages constitutes a critical diagnostic test for A-AION.

5.3.2.8.7. Laboratory investigations. Markedly elevated acutephase responses, i.e., erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most important immediate diagnostic tests in the diagnosis of A-AION and its differentiation from NA-AION (Hayreh et al., 1997a; Hayreh and Zimmerman, 2003a). Although high ESR is traditionally emphasized as a *sine qua non* for

latter detected only on fluorescein fundus angiography. This is because in some cases the central retinal artery and PCA arise by a common trunk from the ophthalmic artery (Fig. 20) (Singh and Dass, 1960a; Hayreh, 1962); in such cases, if arteritis involves the common trunk and causes its thrombosis and occlusion, that results in occlusion of both the PCA (manifesting as A-AION) and the central retinal artery (Hayreh, 1974c; Hayreh et al., 1998a). Thus, in all eyes with central retinal artery occlusion in persons aged 50
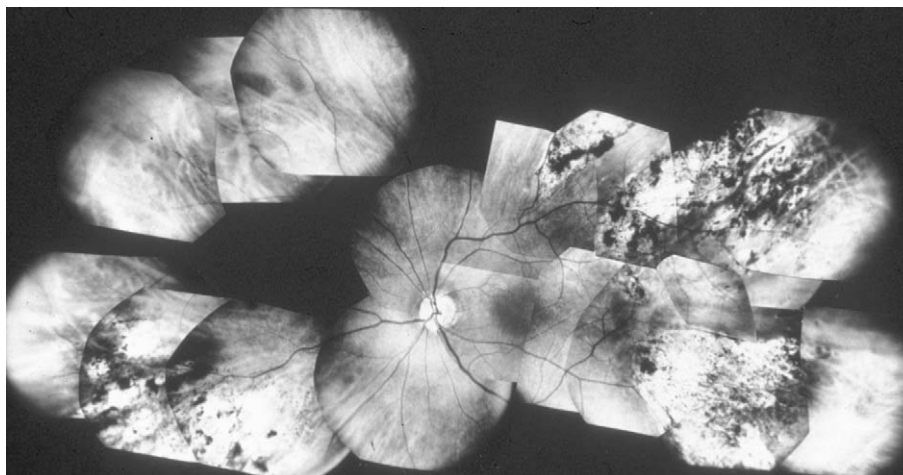

Fig. 21. A composite fundus photograph of left eye of a patient with giant cell arteritis and A-AION. Note optic atrophy and cupping with extensive peripheral chorioretinal lesions.

diagnosis of GCA, there are numerous reports of "normal" or "low" ESR in patients with positive temporal artery biopsy for GCA (Hayreh et al., 1997a; Hayreh and Zimmerman, 2003a). In our series, we had some patients with ESR as low 4–5 mm/h with positive biopsy (Hayreh et al., 1997a; Hayreh and Zimmerman, 2003a). Thus, the rule is normal ESR does not rule out GCA. CRP, on the other hand, emerged from our study as a much more reliable test to diagnose GCA – in our series sensitivity of 100% and specificity of 82% (Hayreh et al., 1997a; Hayreh and Zimmerman, 2003a). A combination of ESR with CRP gave the very best specificity (97%) for detection of GCA. We always use both tests in all our patients, for diagnosis of GCA and monitoring of steroid therapy. Parikh et al. (2006) found sensitivity of ESR 76– 86%, depending on which two formulas they used, and of elevated CRP 97.5%. The sensitivity of the ESR and CRP together was 99%. In that study, two of 119 patients (1.7%) had a "normal" CRP despite an elevated ESR. They recommended that "the use of both tests provides a slightly greater sensitivity for the diagnosis of GCA than the use of either test alone." The difference in sensitivity of CRP found between our series (Hayreh et al., 1997a) and that of Parikh et al. (2006) may be due to the difference in the criterion of "normal" level of CRP, which varies widely among different laboratories – the study by Parikh et al. (2006) was based on multiple centers, while that by us was only at one center.

Other hematological tests, which can help in the diagnosis of GCA include the presence of thrombocytosis, anemia, elevated white blood cell count and low hemoglobin and hematocrit levels (Costello et al., 2004). In conclusion, the combined information provided by ESR, CRP, platelet and white blood cell count and hemoglobin and hematocrit levels is highly useful in diagnosis of GCA, although none of them is individually 100% sensitive and specific.

5.3.3. Management of A-AION

Management of A-AION is actually management of GCA. Kearns (1975) rightly stressed that GCA "ranks as the prime medical emergency in ophthalmology, there being no other disease in which prevention of blindness depends so much on prompt recognition and early treatment." A-AION is the most common cause of visual loss in GCA. Therefore, to prevent blindness in GCA, two things are crucial: (a) early diagnosis of GCA; and (b) immediate and adequate steroid therapy. My studies on GCA have revealed that there is a difference of perspective between rheumatologists and ophthalmologists. For ophthalmologists GCA is a blinding disease with tragic consequences, whereas rheumatologists see mainly a disease with rheumatologic complaints, not very serious. This difference in perspective on GCA has resulted in the controversy about its diagnosis as well as management. This subject is discussed at length elsewhere (Hayreh and Zimmerman, 2003a). Following is a brief summary of that.

5.3.3.1. To establish a definite diagnosis of GCA without delay. This is a most critical step in the management of GCA (Hayreh and Zimmerman, 2003a). Classically the "gold standard" considered for diagnosis of GCA are the five criteria advocated by the American College of Rheumatologists (Hunder et al., 1990): (1) age $\geq$50 years at onset; (2) new onset of localized headache; (3) temporal artery tenderness or decreased temporal artery pulse; (4) elevated ESR (Westergren) $\geq$50 mm/h; and (5) positive temporal artery biopsy for GCA. American College of Rheumatologists stated: "a patient shall be classified as having GCA if at least three of these five criteria are met." The study by Hayreh et al. (1997a), dealing with validity and reliability of various diagnostic criteria for GCA, showed these criteria to be inadequate to prevent blindness in all GCA patients, particularly patients with occult GCA (21% – Hayreh et al., 1998b) who never develop any systemic symptoms of GCA. Thus, American College of Rheumatologists' study criteria are likely to result in some false–negative or false–positive diagnoses of GCA, risking visual loss.

The study by Hayreh et al. (1997a), using positive temporal artery biopsy (TAB) as the definite diagnostic criterion for GCA, showed that the odds of a positive TAB were nine times greater with jaw claudication ($p < 0.0001$), 3.4 times with neck pain ($p = 0.0085$), 2.0 times with ESR (Westergren) 47–107 mm/h relative to those with ESR <47 mm/h ($p = 0.0454$), and 3.2 times with CRP >2.45 mg/dl compared to CRP $\leq$2.45 mg/dl ($p = 0.0208$), and 2.0 times when the patients were aged $\geq$75 years as compared to those <75 years ($p = 0.0105$). Among the other systemic signs and symptoms, the only significant one was anorexia/weight loss ($p = 0.0005$); the rest showed no significant difference from those with negative TAB. So the set of clinical criteria most strongly suggestive of GCA are jaw claudication, CRP >2.45 mg/dl (normal value for CRP in our hematology laboratory is $\leq$0.5 mg/dl), neck pain and ESR $\geq$47 mm/h, in that order. CRP was more sensitive (100%) than ESR (92%), and a combination of ESR with CRP gave the best specificity (97%) for detection of GCA. As discussed above, a "normal ESR" did not rule out GCA. Notably, in our study 21.2% of patients had TAB confirmed GCA without any systemic symptoms or signs of GCA whatsoever, at any stage (i.e. occult GCA) (Hayreh et al., 1998b). To get reliable information about GCA from TAB, we have found that the following steps are essential. (a) The TAB specimen must be at least one inch long; (b) all TAB specimens must be examined by serial sectioning (in one of our cases, only one of 300 sections showed evidence of GCA); (c) if there is a high index of suspicion of GCA, but TAB is negative on one side, TAB should be done on the second side, which was positive in 9% in our series (Hayreh et al., 1997a).

5.3.3.1.1. Differentiation of A-AION from NA-AION. When a patient is diagnosed as having AION, the first crucial step in patients aged 50 and over is to identify immediately whether it is arteritic or non-arteritic. Differential diagnosis of the two types of AION is discussed at length elsewhere (Hayreh, 1990a, 1996; Hayreh and Zimmerman, 2003a) and the following is a brief summary.

Collective information provided by the following criteria helps to differentiate the two types of AION reliably.

5.3.3.1.1.1. Systemic symptoms of GCA. These are discussed in detail above. However, 21.2% with occult GCA have no systemic symptoms of any kind, ever, and visual loss is the sole complaint. Patients with NA-AION have no systemic symptoms of GCA.

5.3.3.1.1.2. Visual symptoms. As discussed above, amaurosis fugax is highly suggestive of A-AION and is extremely rare in NA-AION.

5.3.3.1.1.3. Hematologic abnormalities. Immediate evaluation of ESR and CRP is vital in all patients aged 50 and over. As discussed above, elevated ESR and CRP, particularly CRP, is helpful in the diagnosis of GCA. Patients with NA-AION do not show any of these abnormalities, except when a patient has some other intercurrent systemic disease.

5.3.3.1.1.4. Early massive visual loss. In our study, initial visual acuity of count fingers to no light perception was seen in 54% with A-AION (Hayreh et al., 1998a) and in 14% with NA-AION (Hayreh and Zimmerman, 2008a). This shows that early massive visual loss is extremely suggestive of A-AION. However, the presence of perfectly normal visual acuity does not rule out A-AION (see above).

5.3.3.1.1.5. Chalky white optic disc edema (Figs. 17, 18B and 19A). This is almost diagnostic of arteritic AION and is seen in 69% of A-AION eyes. In NA-AION, chalky white optic disc edema occurs only very rarely with embolic occlusion of the PCA.

5.3.3.1.1.6. A-AION associated with cilioretinal artery occlusion (Fig. 19). This is almost diagnostic of A-AION. As discussed above, this is because both the ONH and cilioretinal artery derive their

blood supply from the PCA, and occlusion of the PCA naturally results in both lesions.

5.3.3.1.1.7. Evidence of PCA occlusion on fluorescein fundus angiography (Figs. 4B,C and 19B). If angiography is performed during the first few days after the onset of A-AION, and the choroid supplied by one or more of the PCAs does not fill, this once again is almost diagnostic of A-AION. However, later on, with the establishment of collateral circulation, this information may be lost. In my studies of NA-AION, such a non-filling of a PCA on angiography has not been seen, except in an extremely rare case when there is embolic occlusion of the PCA (Fig. 4A).

5.3.3.1.1.8. Temporal artery biopsy. This finally establishes the diagnosis and its role has been discussed above.

5.3.3.2. Steroid therapy in GCA to prevent blindness. This is a highly controversial subject, because practically all the available information is from the rheumatological literature. As mentioned above, there is a differing perspective on GCA between rheumatologists and ophthalmologists which has influenced their recommendations on steroid therapy – the regimen advocated by the former primarily concerns managing benign rheumatologic symptoms and signs, whereas the latter confronts the probability of blindness (Hayreh and Zimmerman, 2003a). Moreover, I have found that rheumatologists often tend not to differentiate between polymyalgia rheumatica and GCA in their management. A regimen of steroid therapy, which is adequate to control rheumatologic symptoms and signs and polymyalgia rheumatica, is often totally inadequate to prevent blindness. With this in view, Hayreh and Zimmerman (2003a) did a 27-year prospective study on steroid therapy in GCA, to find a regimen that would prevent visual loss. That study showed marked differences between the rheumatologic and ophthalmic steroid therapy regimens. In the light of information from that study, the following are my guidelines to prevent visual loss.

(a) If there is a reasonable index of suspicion of GCA, as judged from systemic symptoms, high ESR and CRP (particularly high CRP) and sudden visual loss from A-AION or central retinal artery occlusion, high doses of systemic corticosteroid therapy must be started IMMEDIATELY, as an EMERGENCY MEASURE.

The physician should not wait for the result of the TAB because by the time it is available, the patient may have lost further vision irreversibly, in one or both eyes. Every minute counts; it is unwarranted to take chances of losing vision by starting with a small dose; once vision is lost, a subsequent higher dose will not restore it. In my study, the median starting oral Prednisone dose was 80 mg/day, with 40% of patients on ≥100 mg/day.

(b) A high-dose steroid therapy must be maintained until both the ESR and CRP settle down to a stable level which usually takes 2–3 weeks – CRP usually settles much earlier than the ESR (Fig. 22).

(c) After that, gradual tapering down of steroid therapy should be started. Recently, Salvarani et al. (2008) stated that 2–4 weeks after the start of initial dose, "the dose can be gradually reduced each week or every 2 weeks by a maximum of 10% of the total daily dose." The study by Hayreh and Zimmerman (2003a) showed this to be a dangerous formula to prevent blindness. According to that study, a titration of the steroid dosage with the levels of ESR and CRP is the only safe and reliable method for tapering down and follow-up of steroid therapy, and using clinical symptoms and signs of GCA as a guide (often recommended by rheumatologists) is a dangerous practice to prevent blindness (Hayreh, 2000). In my experience of managing several hundred GCA patients during the past four decades, I have never had any GCA patient who developed systemic symptoms even when his ESR and CRP went up significantly after steroid therapy was reduced; ESR and CRP are far more sensitive and reliable than systemic symptoms for managing steroid therapy to prevent visual loss. However, the possibility of systemic symptoms of GCA developing in an extremely rare case while ESR and CRP remain normal on steroid therapy cannot be entirely ruled out – in Medicine there is no such thing as "never". The relapses of GCA frequently mentioned in the rheumatologic literature are the result of using inadequate criteria to monitor and manage steroid therapy and/or inadequate dose of corticosteroids; relapses put the patient at risk of going blind.

(d) Patients with GCA show marked interindividual variation in the dosage of corticosteroids they require, their response to

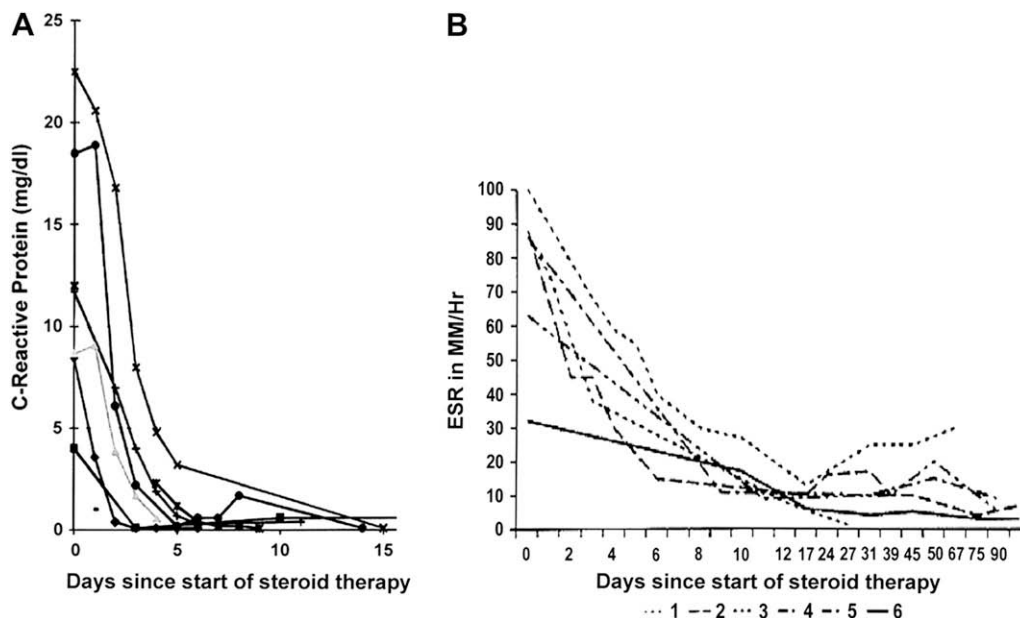**Fig. 22.** Graphs of (**A**) C-reactive protein levels and (**B**) erythrocyte sedimentation rates (ESR) of six patients with giant cell arteritis, showing their initial responses to high dose steroid therapy. (Reproduced from Hayreh and Zimmerman, 2003a).

steroid therapy, and their therapeutic and tapering regimens of steroid therapy, so that therapy must always be individualized. No generalization is possible; NO one size fits all.

(e) Salvarani et al. (2008) recommended that "the necessary duration of glucocorticosteroid therapy is variable, but in most cases it can be discontinued within 1–2 years." This recommendation is based on the widespread but mistaken belief among rheumatologists that GCA is a self-limiting disease and burns itself out within 1–2 years. Following were the relevant findings of the study by Hayreh and Zimmerman (2003a). The median follow-up was 2.43 years, (inter-quartile range of 1– 6 years) and in many cases 20 years or more. This study showed that the statement by Salvarani et al. (2008) and other rheumatologists is not valid as regards visual loss. Some patients went blind after their local rheumatologist stopped steroid therapy after a year or two. In addition, repeat TAB has shown evidence of active GCA after as much as 9 years of steroid therapy (Cohen, 1973; Blumberg et al., 1980; Gouet et al., 1986; Bendo et al., 2008). To keep GCA under good control and prevent blindness, study by Hayreh and Zimmerman (2003a) showed that the vast majority of these patients require a life long low, maintenance dose of corticosteroids, which were found to have no systemic side-effects. In that study, the median time to reach the lowest maintenance dose of Prednisone (at which the ESR and CRP stayed low and stable) was 48.7 months (95% CI: 34.6, 71.4 months), and the median lowest Prednisone dose achieved was 7 mg/day (interquartile range of 1– 16 mg/day). A comparison of patients with and without initial visual loss showed no significant difference in the time to attain the lowest dose. In the study, only 10 (seven without visual loss, three with visual loss) of 145 patients were able to stop the therapy completely and maintain stable ESR and CRP levels without visual loss.

(f) This study found no evidence that intravenous mega-dose steroid therapy was more effective than oral therapy in improving vision (Hayreh et al., 2002) or preventing visual deterioration (Hayreh and Zimmerman, 2003b) due to GCA. My current recommendation for intravenous steroid therapy is to give initially one intravenous mega dose (equivalent to one gram of Prednisone) followed by high-dose (80–120 mg) oral prednisone in any patient who presents with: (i) a history of amaurosis fugax; (ii) complete or marked loss of vision in one eye; or (iii) early signs of involvement of the second eye.

5.3.3.2.1. Risk/benefit ratio of steroid therapy in GCA patents. The concept that systemic steroid therapy is dangerous and must be given in the lowest possible dose and for the minimum period is over-stated in the rheumatologic literature. No doubt, chronic steroid therapy carries a high risk of variable side-effects, but most of them are either tolerable or easily manageable once the patient is fully aware of the alternative, i.e. the risk of going blind in one or both eyes. Once a patient is made aware of the choice between side-effects of steroid therapy versus the risk of going blind, he/she will always choose the therapy, even at the risk of a certain amount of side-effects – I have yet to find a single patient in more than 40 years of dealing with GCA patients who opted against steroid therapy and took the risk of going blind.

To reiterate: in my experience of dealing with several hundred GCA patients for about four decades, I have found that if they are treated promptly and aggressively with an adequate dose of corticosteroids, and reduction of steroid therapy is regulated by using ESR and CRP as the only criteria, not a single patient suffered any further visual loss 5 days after starting adequate steroid therapy – that is testimony to the effectiveness of my steroid therapy regimen.

5.3.3.2.2. Visual prognosis with adequate steroid therapy. In the study of steroid therapy in GCA by Hayreh and Zimmerman (2003a), in spite of start of high dose steroid therapy, only 4% of GCA patients with visual loss showed any visual improvement (Hayreh et al., 2002), and during the first 5 days from the start of the therapy 4% developed further visual loss but there was no further visual loss after 5 days (Hayreh and Zimmerman, 2003b).

5.3.4. Misconceptions about A-AION and GCA and preventing visual loss

1. That to diagnose GCA, the patient must have systemic symptoms and signs of GCA. A study showed that 21% of GCA patients have no systemic symptoms and signs whatsoever and the only presenting sign is visual loss, i.e., occult GCA (Hayreh et al., 1998b).
2. That to diagnose GCA, the patient must have elevated ESR. As discussed above, it has been shown that normal ESR does not rule out GCA.
3. That steroid therapy can be tapered according to a set regimen (Salvarani et al., 2008). As discussed above, it has been shown that there is marked interindividual variation in the tapering regimen of steroid therapy and NO one size fits all.
4. That steroid therapy can be regulated by using clinical symptoms and signs of GCA. That is not valid to prevent visual loss. The only reliable method is to use ESR and CRP as the guideline.
5. That steroid therapy can be stopped after 1–2 years because the disease burns itself out. That is not true at all. A vast majority of patients require life-long steroid therapy to prevent visual loss.

5.4. Posterior ischemic optic neuropathy

Hayreh (1981b) first described this clinical entity in 1981. Since then, many reports have appeared, but they are all anecdotal in nature, except for three series – 14 cases by Isayama et al. (1983), 72 by Sadda et al. (2001) and 42 by Hayreh (2004b). This shows that PION is much less common than AION; this may be due to combination of various factors (Hayreh, 2004b). Since the diagnosis of PION, and especially non-arteritic PION, is usually hard to make with certainty, it is difficult to ascertain its true incidence. When Hayreh (1981b) first described this as a distinct clinical entity, he stressed that it is a diagnosis of exclusion. It should be made only after all other possibilities have been carefully ruled out, e.g., macular and retinal lesions, NA-AION, retrobulbar optic neuritis, compressive optic neuropathy, other optic disc and optic nerve lesions, neurological lesions, hysteria, even malingering, and a host of other lesions.

5.4.1. Classification

Etiologically, PION can be classified into three types: (1) arteritic PION (A-PION) due to GCA; (2) non-arteritic PION (NA-PAON) due to causes other than GCA; and (3) surgical PION as a complication of a surgical procedure. Incidence of various types of PION reported in the three large series varies widely. All 14 cases reported by Isayama et al. (1983) had NA-PION. Among the 72 patients in Sadda et al.'s (2001) series, 53% had NA-PION, 8% A-PION and 39% surgical PION. In Hayreh (2004b) study, of the 42 patients, 65% had NA-PION, 28% A-PION and 7% surgical PION. The clinical findings in any PION study depend upon not only the number of patients but also the various types of PION.

5.4.2. Pathogenesis

This is discussed at length elsewhere (Hayreh, 2004b). Briefly, it is as follows.

5.4.2.1. Arteritic PION. This is due to GCA when arteritis involves orbital arteries, which supply the posterior part of the optic nerve (Fig. 2). A-PION occurs much less commonly than A-AION. For example, in the study by Hayreh et al. (1998a) of 123 eyes with visual loss due to GCA, A-AION was seen in 94 eyes and A-PION in only seven.

5.4.2.2. Non-arteritic PION. An association between NA-PION and a variety of systemic diseases has been reported in the literature. The common diseases include arterial hypertension, diabetes mellitus, arteriosclerosis, atherosclerosis, and marked arterial hypotension, and there have been anecdotal case reports of PION associated with many other diseases (Sadda et al., 2001; Hayreh, 2004b). In Hayreh's (2004b) series of 42 consecutive patients with PION, when the prevalence of systemic diseases was compared to the control population, there was a significantly higher prevalence of arterial hypertension, diabetes mellitus, ischemic heart disease, cerebrovascular disease, carotid artery and peripheral vascular disease and migraine in NA-PION patients. Thus, the pathogenesis of NA-PION, like NA-AION (Hayreh et al., 1994b), is multifactorial in nature, with a variety of systemic diseases, other vascular risk factors and/or local risk factors predisposing an optic nerve to develop PION; defective autoregulation of the optic nerve may also play a role. Finally, some precipitating risk factor acts as the "last straw" to produce PION.

5.4.2.3. Surgical PION. This clinical entity has also been called postoperative (Roth and Barach, 2001) or perioperative (Sadda et al., 2001) PION. I have used the term "surgical PION" because it is more inclusive. Surgical PION usually tends to cause bilateral massive visual loss or even complete blindness, which is usually permanent; therefore, it has great medicolegal importance. A large number of surgical PION cases have been reported in the literature (mostly anecdotal), almost invariably associated with prolonged systemic surgical procedures, for a variety of conditions, including spinal and other orthopedic surgical procedures, radical neck dissection, venous graft in extremities, coronary artery bypass, hip surgery, nasal surgery, thoracotomy for hemothorax, penetrating thoracoabdominal injury, cataract surgery, and strabismus surgery (Hayreh, 2004b). Sadda et al. (2001) reported 28 patients following a variety of procedures.

The pathogenesis of surgical PION is discussed at length elsewhere (Hayreh, 2004b). Briefly, it is multifactorial in nature. The main factors include severe and prolonged arterial hypotension (due to prolonged general anesthesia, surgical trauma and massive blood loss), hemodilution from administration of a large amount of intravenous fluids to compensate for the blood loss, orbital and periorbital edema, chemosis and anemia, and rarely even direct orbital compression by prone position.

Several authors have equated visual loss due to surgical PION to that seen in patients with post-hemorrhagic amaurosis (Hayreh, 1987), i.e. visual loss after recurrent systemic hemorrhages. The two are actually very different in nature, because in post-hemorrhagic amaurosis visual loss develops: (a) hours, days or even weeks after systemic bleeding; (b) very rarely after a single hemorrhage; (c) when hemoglobin and blood pressure may be within normal limits; and (d) usually during sleep, or worsens during sleep (Hayreh, 1987) The pathogenesis of post-hemorrhagic amaurosis is discussed in detail elsewhere (Hayreh, 1987). Briefly, it is as follows. Considerable evidence has accumulated that blood loss, with or without arterial hypotension, causes increase in release of renin and endogenous vasoconstrictor agents (e.g., angiotensin, epinephrine, and vasopressin) because of activation of sympathoadrenergic system and vasomotor center. Our experimental studies on renovascular malignant hypertension indicate that endogenous vasoconstrictor agents produce choroidal ischemia and NA-AION (Hayreh et al., 1986a,b). In view of all the available evidence, it is postulated that in the production of NA-AION after blood loss, release of endogenous vasoconstrictor agents is probably a very important factor, with arterial hypotension an additional factor; increased platelet aggregation may also play a role (Hayreh, 1987).

5.4.3. Clinical features of PION

5.4.3.1. Age and gender. PION, like NA-AION, is seen mostly in the middle-aged and elderly population but no age is immune to it. In Hayreh's (2004b) series, median age was 61.5 years in NA-PION, 73.4 in A-PION, and 77.3 in surgical PION. The youngest patient in his series with NA-PION was 20 years old; in Sadda et al.'s (2001) series 18 years old; and Gerber et al.'s (1992) reported this in a 15-year old. A-PION, like A-AION, is more common in women than men.

5.4.3.2. Symptoms. Clinically, patients with A-PION and NA-PION typically present with acute, painless visual loss in one or both eyes, sometimes discovered upon waking up in the morning. In some eyes, it may initially be progressive. Patients with surgical PION discover visual loss as soon as they are alert postoperatively, which may be several days after surgery. Surgical PION usually tends to cause bilateral massive visual loss or even complete blindness, which is usually permanent.

5.4.3.3. Visual acuity. This depends upon the type of PION. In Hayreh's (2004b) series, in NA-PION, it was 20/20–20/25 in 17%, better than 20/40 in 20%, 20/200 or worse in 69%; in A-PION 29, 43 and 50% respectively; and in surgical PION only light perception.

5.4.3.4. Visual fields. A wide variety of optic nerve related visual field defects have been reported in PION; their type varies with the type of PION (Sadda et al., 2001; Hayreh, 2004b). In the study by Hayreh (2004b), the most common visual field defect was central visual loss, alone or in combination with other types of visual field defects (Fig. 23). Central visual field defect was present in 84% in NA-PION, 69% in A-PION. A small number of PION eyes show the reverse pattern, i.e., the central field was normal with marked loss of peripheral fields (Fig. 24).

5.4.3.4.1. Pathogenesis of various types of visual field defects seen in PION. To understand these two totally opposite patterns of visual field defects, it is essential to have a grasp of: (a) the arrangement of the optic nerve fibers; and (b) vascular pattern in the posterior part of the optic nerve. The optic nerve fibers rearrange themselves as they travel posteriorly in the optic nerve; for example, the macular fibers lie in the temporal part of the ONH but in the central part of the optic nerve posteriorly (Duke-Elder and Wybar, 1961). The implication of this is that segmental ischemia of the ONH is likely to produce a visual field defect very different from that produced by segmental ischemia in the posterior part of the optic nerve.

In most eyes, the blood supply to the posterior part of the optic nerve is by the peripheral vascular system only, with no separate axial blood supply (Fig. 1B). That makes the axial part of the optic nerve more susceptible to ischemic damage than the peripheral part. That may explain the common occurrence of central visual field defect with intact peripheral field in PION (Fig. 23). In about 10% of nerves, by contrast, the axial region of the posterior part of the optic nerve is supplied by an intraneural branch of the central retinal artery (Fig. 3) (Hayreh, 1958, 2004b), and that helps to protect the axial region from ischemic damage. That may explain the preservation of a tunnel-like central field in PION in spite of loss of peripheral visual field (Fig. 24).

Since each collateral branch supplies a localized area of variable size in the posterior optic nerve (Figs. 1B and 2), occlusion of different collaterals can result in a variety of visual field defects
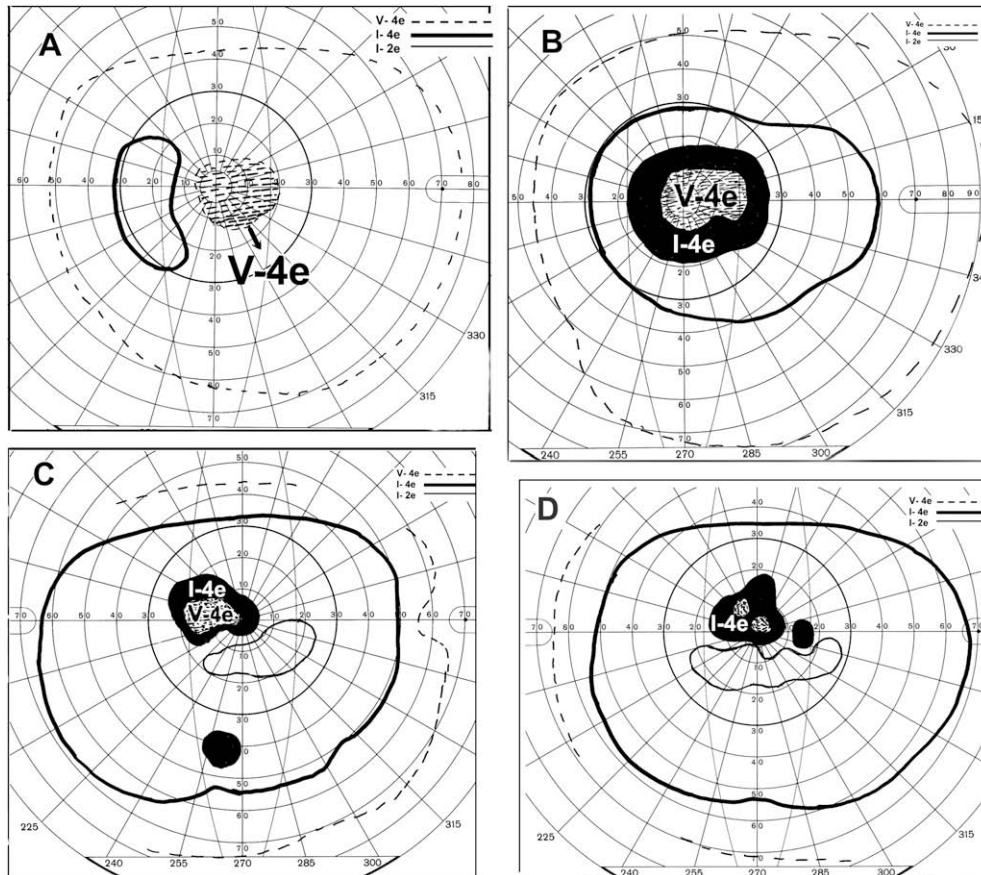
Fig. 23. Four visual fields showing varying sizes and densities of central scotoma and other field defects, with normal peripheral visual fields in non-arteritic PION. (Reproduced from Hayreh, 2004b).

depending upon their area of supply and the origin of the optic nerve fibers from the retina in that region. Isayama and Takahashi (1983) in their histopathological study in PION found that the ischemic lesions could be located in the transverse, peripheral, altitudinal or axial areas of the nerve. That would explain the different types of visual field defects seen in PION.

5.4.3.5. Ophthalmic evaluation. Initially, apart from relative afferent pupillary defect in unilateral PION, the anterior segment, intraocular pressure, and optic disc and fundus are normal on

ophthalmoscopy and fluorescein fundus angiography. The disc develops pallor generally within 6–8 weeks, usually more marked in the temporal part. Rarely the optic disc may develop cupping in NA-PION (Hayreh, 2004b). The criteria to differentiate arteritic from non-arteritic PION are basically the same as those for arteritic and non-arteritic AION discussed above, except that the optic disc and fundus are initially normal in both types in PION.

5.4.3.6. Diagnosis of PION. A combination of the following findings is highly suggestive of PION: (a) sudden onset of visual deterioration,
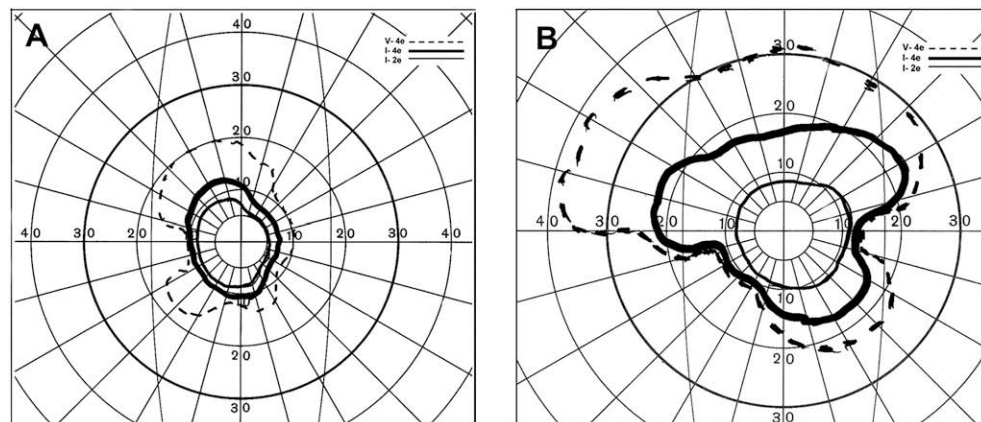

Fig. 24. Visual fields of (**A**) right and (**B**) left eyes with arteritic PION, showing markedly constricted central visual fields, with complete loss of peripheral fields in both eyes. (Reproduced from Hayreh, 2004b).

with or without deterioration of central visual acuity; (b) optic nerve-related visual field defects in the involved eye; (c) presence of a relative afferent pupillary defect in the involved eye in patients with a perfectly normal fellow eye; (d) optic disc and fundus initially normal on ophthalmoscopy and fluorescein fundus angiography; (e) no other ocular, orbital or neurological abnormality to explain the visual loss; and (f) development of optic disc pallor, usually within 6–8 weeks. The diagnosis of surgical PION, on the other hand, is relatively straightforward; dramatic visual loss noticed as soon as the patient is alert enough after a major surgical procedure, with the above clinical findings. As I stressed in my original paper (Hayreh, 1981b) on PION, it is a diagnosis of exclusion.

5.4.3.7. Bilateral PION. In the series of Sadda et al. (2001) PION was bilateral in 21% of NA-PION, 50% of A-PION and 54% of surgical PION. In Hayreh's (2004b) series, the corresponding incidence was 25, 17 and 75% respectively.

5.4.4. Management of PION

This depends upon the type of PION. In all cases other than surgical PION, as in AION, the most important first step in persons aged 50 years or older is always to rule out GCA (Hayreh, 1990a; Hayreh et al., 1998a).

5.4.4.1. Arteritic PION. Management is similar to that of A-AION discussed above. There is usually no visual improvement with systemic steroid therapy.

5.4.4.2. Non-arteritic PION. The role of systemic steroid therapy in PION was evaluated in the study by Hayreh (2004b). That showed that the eyes of patients treated with high dose systemic steroid therapy during the very early stages of the disease showed significant improvement in visual acuity and visual field, compared to untreated eyes. In addition, the magnitude of visual acuity and visual field improvement was much greater in the treated group than the untreated group. Thus, it is clear that aggressive systemic steroid therapy has a beneficial effect on visual function during the very early stages of the disease. However, spontaneous improvement in visual acuity and visual field may also occur to some extent in some eyes without steroid therapy. Sadda et al. (2001) reported that visual acuity improved in 34%, remained stable in 28% and worsened in 38%; in that study, however, there is no mention whether any of their patients were treated or not.

In the management of these patients, since systemic risk factors may play a part in the development of NA-PION, one should try to reduce as many risk factors as possible, to reduce the risk of second eye involvement.

5.4.4.3. Surgical PION. Basically, the management amounts to prophylactic measures to prevent development, because once the visual loss occurs, it is usually bilateral, severe and irreversible. No treatment has been found to be effective to recover or improve the lost vision. Prophylactic measures during surgery include avoiding: arterial hypotension, excessive fluid replacement and hemodilution, pressure on the eyeball and orbit, and dependent position of the head, as well as shortening the duration of surgery to the minimum. Since systemic cardiovascular risk factors may predispose a patient to a higher risk of developing surgical PION, it may be advisable to consider those factors in the decision to perform surgery.

5.4.5. Visual prognosis in PION

This varies with the type of PION. Eyes with NA-PION treated with high dose steroid therapy at onset showed significantly greater visual improvement than untreated patients (Hayreh, 2004b). Patients with A-PION, if treated urgently and aggressively with high dose steroid therapy, showed no improvement in vision but also showed no further visual loss. Patients with surgical PION usually suffer severe, often bilateral and irreversible visual loss; this does not respond to steroid therapy (Sadda et al., 2001; Hayreh, 2004b).

6. Conclusions and future directions

It is now clear that ischemic optic neuropathy is not one disease but a spectrum of several different types, each with its own etiology, pathogenesis and management. Each must be considered separately. Overall, they constitute one of the major causes of blindness or seriously impaired vision, yet there is marked confusion and controversy on their pathogeneses, clinical features and especially their management. This is because the subject is plagued by misconceptions about many fundamental aspects, discussed in this review. The ophthalmologist needs to be aware of these misconceptions, and also to be armed with the most comprehensive, up-to-date basic scientific information. The basic sciences are the foundation of Medicine. During the recent past, newly emerging knowledge on basic and clinical aspects of the various types of ischemic optic neuropathy has improved our knowledge of their etiology, clinical features and management. Advances in knowledge of the various factors that influence the optic nerve circulation, and also the various systemic and local risk factors which play important roles in the development of various types of ischemic optic neuropathy have given us a better understanding of their pathogenesis. This knowledge should help us not only to manage them better but also to reduce their incidence. For example, clinically, the evidence that about 40% of NA-AION eyes experience spontaneous improvement in visual acuity, and that systemic steroid therapy during early stages of both NA-AION and NA-PION has a significant beneficial effect on the visual outcome are encouraging signs for the better management of these blinding diseases. Knowledge is ever advancing, and with advances in basic scientific knowledge we should be able to manage these blinding diseases more and more effectively.

Conflict of interest statement

The author has no conflict of interest.

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